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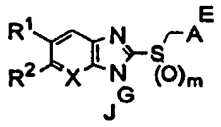
(54)Title: THIOBENZIMIDAZOLE DERIVATIVES

(54)発明の名称 チオベンズイミダゾール誘導体



(1)

(57) Abstract

Thiobenzimidazole derivatives represented by general formula (1) or pharmaceutically acceptable salts thereof which have a potent human chymase inhibitory activity and, therefore, are usable as clinically applicable preventives and/or remedies for various diseases in which human chymase participates.

DESCRIPTION

THIOBENZIMIDAZOLE DERIVATIVES

Technical Field

The present invention relates to thiobenzimidazole derivatives represented by the formula (1) and, more specifically, thiobenzimidazole derivatives useful as inhibitors of human chymase activity.

Background Art

Chymase is one of the neutral proteases present in mast cell granules, and is deeply involved in a variety of biological processes in which mast cells participate. Various effects have been reported including, for example, the promotion of degranulation from mast cells, the activation of interleukin-1β (IL-1β), the activation of matrix protease, the decomposition of fibronectin and type IV collagen, the promotion of the release of transforming growth factor-β (TGF-β), the activation of substance P and vasoactive intestinal polypeptide (VIP), the conversion of angiotensin I (Ang I) to Ang II, the conversion of endothelin, and the like.

The above indicates that inhibitors of said chymase activity may be promising as preventive and/or therapeutic agents for diseases of respiratory organs such as bronchial asthma, inflammatory/allergic diseases, for example allergic rhinitis, atopic dermatitis, and urticaria; diseases of circulatory organs, for example sclerosing vascular lesions, intravascular stenosis, disturbances of peripheral circulation, renal failure, and cardiac failure; diseases of bone/cartilage metabolism such as rheumatoid arthritis and osteoarthritis, and the like.

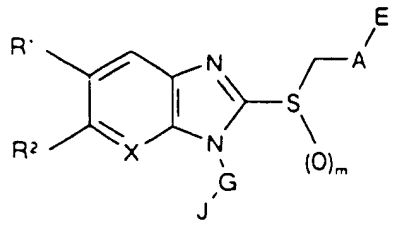
As inhibitors of chymase activity, there are known triazine derivatives (Japanese Unexamined Patent

Publication (Kokai) No. 8-208654); hydantoin derivatives (Japanese Unexamined Patent Publication (Kokai) No. 9-31061); imidazolidine derivatives (PCT Application WO 96/04248); quinazoline derivatives (PCT Application WO 97/11941); heterocyclic amide derivatives (PCT Application WO 96/33974); and the like. However, the structures of these compounds are entirely different from those of the compounds of the present invention.

On the other hand, an art related to the compounds of the present invention is disclosed in U.S. Pat. No. 5,124,336. Said specification describes thiobenzimidazole derivatives as having an activity of antagonizing thromboxane receptor. The specification, however, makes no mention of the activity of said compounds to inhibit human chymase.

Disclosure of the Invention

1. A thiobenzimidazole derivative represented by the following formula (1):



(1)

wherein,

R^1 and R^2, simultaneously or independently of each other, represent a hydrogen atom, a halogen atom, a trihalomethyl group, a cyano group, a hydroxy group, an

alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R^1 and R^2 together form $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ or $-CH_2-CH_2-CH_2-$, in which the carbons may be substituted with one or a plurality of alkyl groups having 1 to 4 carbons;

A represents a single bond, a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, in which the substituent represents a halogen atom, OH, NO_2, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group;

E represents $COOR^3$, SO_3R^3, $CONHR^3$, SO_2NHR^3, a tetrazole group, a 5-oxo-1,2,4-oxadiazole group or a 5-oxo-1,2,4-thiadiazole group in which R^3 represents a hydrogen atom, or a linear or branched alkyl group having 1 to 6 carbons;

G represents a substituted or unsubstituted, linear or branched alkylene group having 1-6 carbons that may be interrupted with one or a plurality of O, S, SO_2, and NR^3, in which R^3 is as defined above and the substituent represents a halogen atom, OH, NO_2, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or

branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a trihalomethyl group, a trihalomethoxy group, a phenyl group, or an oxo group;

m represents an integer of 0 to 2;

when m is 0 and A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 3 to 6 carbons, a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring;

when m is 0 and A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring; or

when m is 0 and A is a single bond or when m is 1 or 2, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, in which the substituent represents a halogen atom, OH, NO_2, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be

joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a substituted or unsubstituted anilide group, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, a $COOR^3$ group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group; and

X represents CH or a nitrogen atom;

or a medically acceptable salt thereof (hereinafter referred to as "the thiobenzimidazole derivative of the present invention").

2. The thiobenzimidazole derivative characterized in that, in the above formula (1), A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, or a medically acceptable salt thereof.

3. The thiobenzimidazole derivative characterized in that, in the above formula (1), A is a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, or a medically acceptable salt thereof.

4. The thiobenzimidazole derivative characterized in that, in the above formula (1), m is 1, or a medically acceptable salt thereof.

5. The thiobenzimidazole derivative characterized in that, in the above formula (1), m is 2, or a medically acceptable salt thereof.

6. The thiobenzimidazole derivative characterized in that, in the above formula (1), m is 0, A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, and J is a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, or a medically acceptable salt thereof.

7. The thiobenzimidazole derivative characterized in that, in the above formula (1), m is 0, A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, and J is a substituted or unsubstituted aryl group having 6 to 11 carbons or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, or a medically acceptable salt thereof.

8. The thiobenzimidazole derivative characterized in that, in the above formula (1), G is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2CO-$, $-CH_2CH_2O-$, $-CH_2CONH-$, $-CO-$, $-SO_2-$, $-CH_2SO_2-$, $-CH_2S-$ or $-CH_2CH_2S-$, or a medically acceptable salt thereof.

9. The thiobenzimidazole derivative characterized in that, in the above formula (1), R^1 and R^2 simultaneously represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R^1 and R^2, independently of each other, represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, a trihalomethyl group, a cyano group, or a hydroxy group, or a medically acceptable salt thereof.

10. The thiobenzimidazole derivative characterized in that, in the above formula (1), E represents COOH or a tetrazole group, or a medically acceptable salt thereof.

11. The thiobenzimidazole derivative characterized in that, in the above formula (1), X represents CH, or a medically acceptable salt thereof.

12. A thiobenzimidazole derivative characterized by having an activity of inhibiting human chymase, or a medically acceptable salt thereof.

13. A pharmaceutical composition comprising an at least one thiobenzimidazole derivative or a medically acceptable salt thereof and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition which is a preventive and/or therapeutic agent for a disease.

15. A preventive and/or therapeutic agent wherein said disease is an inflammatory disease, an allergic disease, a disease of respiratory organs, a disease of circulatory organs, or a disease of bone/cartilage metabolism.

Best Mode for Carrying Out the Invention

The present invention will now be explained in more detail below.

The above definitions concerning the substituents of the compounds of formula (1) of the present invention are as follows:

R^1 and R^2, simultaneously or independently of each other, represent a hydrogen atom, a halogen atom, a trihalomethyl group, a cyano group, a hydroxy group, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R^1 and R^2 together form $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ or $-CH_2-CH_2-CH_2-$, in which the carbons may be substituted with one or a plurality of alkyl groups having 1 to 4 carbons. As the alkyl group having 1 to 4 carbons, there can be mentioned a methyl group, an ethyl group, a (n, i-) propyl group and a (n, i, s, t-) butyl group, and preferably a methyl group may be mentioned. Preferably R^1 and R^2 simultaneously represent a hydrogen atom, a halogen atom, an alkyl group

having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R^1 and R^2, independently of each other, represent a hydrogen atom, a halogen atom, a trihalomethyl group, a cyano group, a hydroxy group, an alkyl group having 1 to 4 carbons, or an alkoxy group having 1 to 4 carbons. As the halogen atom, as used herein, there can be mentioned a fluorine atom, a chlorine atom, a bromine atom and the like, and preferably a chlorine atom and a fluorine atom may be mentioned. As the alkyl group having 1 to 4 carbons, there can be mentioned a methyl group, an ethyl group, a (n, i-) propyl group and a (n, i, t-) butyl group, and preferably a methyl group may be mentioned. As the alkoxy group having 1 to 4 carbons, there can be mentioned a methoxy group, an ethoxy group, a (n, i-) propyloxy group and a (n, i, s, t-) butyloxy group, and preferably a methoxy group may be mentioned.

A represents a single bond, a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons **that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring (sometimes referred to as being on the ring). Preferably, there can be mentioned a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring. As the substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, there can be mentioned a methylene group, an ethylene group, a (n, i-) propylene group and a (n, i, t-) butylene group, and preferably an ethylene group may be mentioned. As the substituted or unsubstituted arylene group having 6 to 11 carbons, there can be mentioned a phenylene group, an**

indenylene group and a naphthylene group etc., and preferably a phenylene group may be mentioned. As the substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms **in** the ring, there can be mentioned a pyridilene group, a furanylene group, a thiophenylene group, an imidazolene group, a thiazolene group, a pyrimidilene group, an oxazolene group, an isoxazolene group, a benzphenylene group, a benzimidazolene group, a quinolilene group, an indolene group, a benzothiazolene group and the like, and preferably a pyridilene group, a furanylene group, and a thiophenylene group may be mentioned.

Furthermore, as the substituent, as used herein, there can be mentioned a halogen atom, OH, NO_2, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons in which the substituent may be joined to each other at adjacent sites via an acetal bond, a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a trihalomethyl group, a trihalomethoxy group, a phenyl group, or a phenoxy group that may be substituted with one or more halogen atoms. They may be independently substituted at any one or more sites of the ring or the alkylene group. Specifically, there can be mentioned OH, a chloro group, a bromo group, a nitro group, a methoxy group, a cyano group, a methylenedioxy group, a trifluoromethyl group, a methyl group, an ethyl group, a (n, i-) propyl group, a (n, i, t-) butyl group, and the like.

As E, there can be mentioned $COOR^3$, SO_3R^3, $CONHR^3$, SO_2NHR^3, a tetrazole group, a 5-oxo-1,2,4-oxadiazole group or a 5-oxo-1,2,4-thiadiazole group, and preferably $COOR^3$ or a tetrazole group may be mentioned. As R^3 as

used herein, there can be mentioned a hydrogen atom or a linear or branched alkyl group having 1 to 6 carbons, and preferably a hydrogen atom, a methyl group, an ethyl group, or a t-butyl group may be mentioned, and most preferably a hydrogen atom may be mentioned.

G represents a substituted or unsubstituted, linear or branched alkyl group having 1 to 6 carbons that may be interrupted with one or a plurality of O, S, SO_2, and NR^3, in which R^3 is as defined above and the substituent represents a halogen atom, OH, NO_2, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a trihalomethyl group, a trihalomethoxy group, a phenyl group, or an oxo group. Specifically, there can be mentioned $-CH_2-$, $-CH_2CH_2-$, $-CH_2CO-$, $-CH_2CH_2O-$, CH_2CONH-, $-CO-$, $-SO_2-$, $-CH_2SO_2-$, $-CH_2S-$, $-CH_2CH_2S-$ and the like, and preferably $-CH_2-$, $-CH_2CH_2-$, $-CH_2CO-$ or $-CH_2CH_2O-$ may be mentioned.

m represents an integer of 0 to 2, and preferably 0 or 2 may be mentioned.

When m is 0 and A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 3 to 6 carbons, a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring. Preferably, a substituted aryl group having 10 to 11 carbons and a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring may be mentioned. As the substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, there can be mentioned

a (n, i-) propyl group, a (n, i, s, t-) butyl group, a (n, i, ne, t-) pentyl group and a cyclohexyl group. As the substituted or unsubstituted aryl group having 7 to 9 carbons, there can be mentioned an indenyl group, and as the substituted aryl group having 10 to 11 carbons, there can be mentioned a naphthyl group. As the substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, there can be mentioned a pyridyl group, a furanyl group, a thiophenyl group, an imidazole group, a thiazole group, a pyrimidine group, an oxazole group, an isoxazole group, a benzofurane group, a benzimidazole group, a quinoline group, an isoquinoline group, a quinoxaline group, a benzoxadiazole group, a benzothiadiazole group, an indole group, a N-methylindole group, a benzothiazole group, a benzothiophenyl group, a benzisoxazole group and the like, and preferably a benzothiophenyl group or a N-methylindole group may be mentioned.

When m is 0 and A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, and preferably a substituted or unsubstituted aryl group having 6 to 11 carbons and a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring may be mentioned. As the substituted or unsubstituted aryl group having 6 to 11 carbons, there

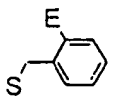
can be mentioned a phenyl group, an indenyl group, a naphthyl group and the like, and preferably a phenyl group or a naphthyl group may be mentioned. As the substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons and as the substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, there can be mentioned those described above. As the substituent as used herein, there can be mentioned a halogen atom, OH, NO_2, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a substituted or unsubstituted anilide group, a trihalomethyl group, a trihalomethoxy group, a phenyl group, or a phenoxy group that may be substituted with one or more halogen atoms. They may be independently substituted at any one or more sites of the ring or the alkyl group. Specifically, there can be mentioned OH, a chloro group, a bromo group, a nitro group, a methoxy group, a cyano group, a methylenedioxy group, a trifluoromethyl group, a trifluoromethoxy group, a methyl group, an ethyl group, a (n, i-) propyl group, a (n, i, s, t-) butyl group, an anilide group and the like.

X represents CH or a nitrogen atom, and preferably CH may be mentioned.

As the compound of formula (1), specifically those described in Tables 1 to 40 are preferred. Most preferred among them are compounds Nos. 37, 50, 63, 64, 65, 84, 115, 117, 119, 121, 123, 130, 143, 147, 168, 174, 256, 264, 272, 311, 319, 320, 321, 324, 349, 352, 354, 355, 358, 364, 380, 392, 395, 398, 401, 402, 444, 455,

459, 460, 506, 863, 866, and 869.

A1 to A21 and J1 to J85 described in Tables 1 to 40 are the groups shown below, in which E and G are as described above.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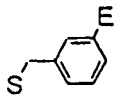
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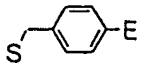
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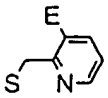
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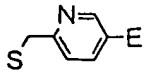
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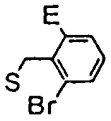
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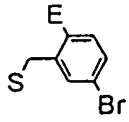
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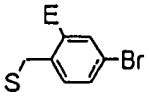
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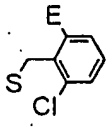
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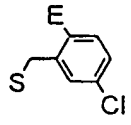
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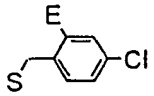
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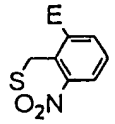
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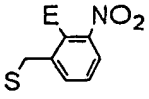
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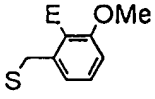
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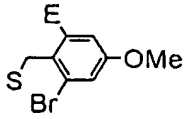
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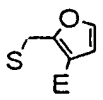
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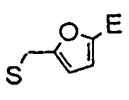
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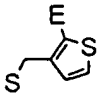
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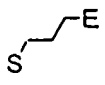
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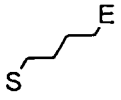
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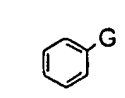

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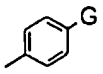

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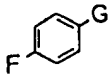

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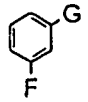

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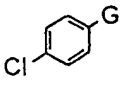

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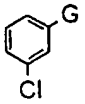

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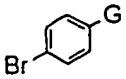

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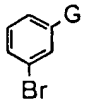

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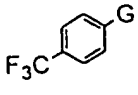

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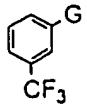

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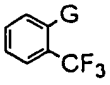

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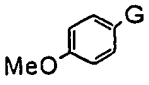

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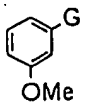

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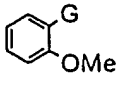

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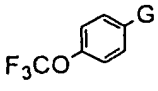

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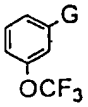

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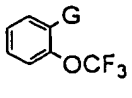

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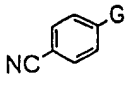

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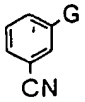

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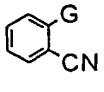

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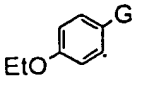

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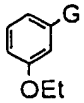

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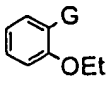

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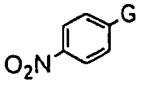

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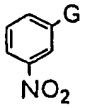

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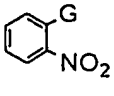

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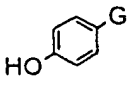

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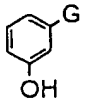

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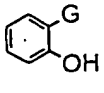

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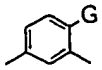

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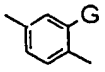

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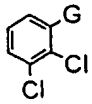

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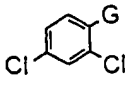

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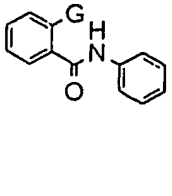
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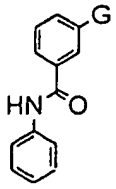
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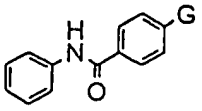
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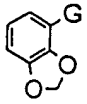
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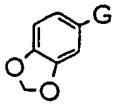
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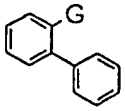
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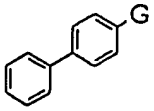
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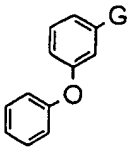
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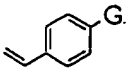
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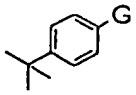
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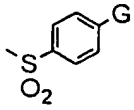
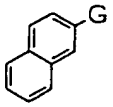

J61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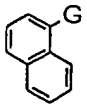
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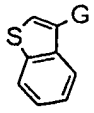
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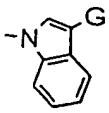
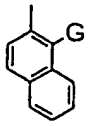
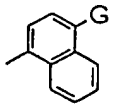
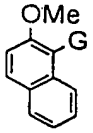
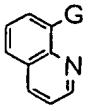

J65


J66


J67


J68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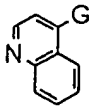
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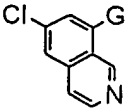
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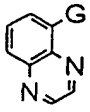
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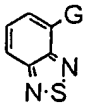
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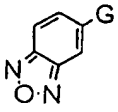
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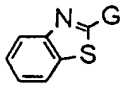

J75


J76


J77


J78


J79


J80


J81


J82


J83


J84


J85

Table 1

Compound No.	R'	R'	SCH_2-A	E	G	J	m	X
1	H	H	A1	COOH	CH_2CH_2	J1	0	CH
2	H	H	A1	COOH	CH_2	J2	0	CH
3	H	H	A1	COOH	CH_2	J3	0	CH
4	H	H	A1	COOH	CH_2	J4	0	CH
5	H	H	A1	COOH	CH_2	J5	0	CH
6	H	H	A1	COOH	CH_2	J6	0	CH
7	H	H	A1	COOH	CH_2	J7	0	CH
8	H	H	A1	COOH	CH_2	J8	0	CH
9	H	H	A1	COOH	CH_2	J9	0	CH
10	H	H	A1	COOH	CH_2	J10	0	CH
11	H	H	A1	COOH	CH_2	J11	0	CH
12	H	H	A1	COOH	CH_2	J12	0	CH
13	H	H	A1	COOH	CH_2	J13	0	CH
14	H	H	A1	COOH	CH_2	J14	0	CH
15	H	H	A1	COOH	CH_2	J15	0	CH
16	H	H	A1	COOH	CH_2	J16	0	CH
17	H	H	A1	COOH	CH_2	J17	0	CH
18	H	H	A1	COOH	CH_2	J18	0	CH
19	H	H	A1	COOH	CH_2	J19	0	CH
20	H	H	A1	COOH	CH_2	J20	0	CH
21	H	H	A1	COOH	CH_2	J21	0	CH
22	H	H	A1	COOH	CH_2	J22	0	CH
23	H	H	A1	COOH	CH_2	J23	0	CH
24	H	H	A1	COOH	CH_2	J24	0	CH
25	H	H	A1	COOH	CH_2	J25	0	CH

Table 2

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
26	H	H	A1	COOH	CH_2	J26	0	CH
27	H	H	A1	COOH	CH_2	J27	0	CH
28	H	H	A1	COOH	CH_2	J28	0	CH
29	H	H	A1	COOH	CH_2	J29	0	CH
30	H	H	A1	COOH	CH_2	J30	0	CH
31	H	H	A1	COOH	CH_2	J31	0	CH
32	H	H	A1	COOH	CH_2	J32	0	CH
33	H	H	A1	COOH	CH_2	J33	0	CH
34	H	H	A1	COOH	CH_2	J34	0	CH
35	H	H	A1	COOH	CH_2	J35	0	CH
36	H	H	A1	COOH	CH_2	J36	0	CH
37	H	H	A1	COOH	CH_2	J37	0	CH
38	H	H	A1	COOH	CH_2	J38	0	CH
39	H	H	A1	COOH	CH_2	J39	0	CH
40	H	H	A1	COOH	CH_2	J40	0	CH
41	H	H	A1	COOH	CH_2	J41	0	CH
42	H	H	A1	COOH	CH_2	J42	0	CH
43	H	H	A1	COOH	CH_2	J43	0	CH
44	H	H	A1	COOH	CH_2	J44	0	CH
45	H	H	A1	COOH	CH_2	J45	0	CH
46	H	H	A1	COOH	CH_2	J46	0	CH
47	H	H	A1	COOH	CH_2	J47	0	CH
48	H	H	A1	COOH	CH_2	J48	0	CH
49	H	H	A1	COOH	CH_2	J49	0	CH
50	H	H	A1	COOH	CH_2	J50	0	CH

Table 3

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
51	H	H	A1	COOH	CH_2	J51	0	CH
52	H	H	A1	COOH	CH_2	J52	0	CH
53	H	H	A1	COOH	CH_2	J53	0	CH
54	H	H	A1	COOH	CH_2	J54	0	CH
55	H	H	A1	COOH	CH_2	J55	0	CH
56	H	H	A1	COOH	CH_2	J56	0	CH
57	H	H	A1	COOH	CH_2	J57	0	CH
58	H	H	A1	COOH	CH_2	J58	0	CH
59	H	H	A1	COOH	CH_2	J59	0	CH
60	H	H	A1	COOH	CH_2	J60	0	CH
61	H	H	A1	COOH	CH_2	J61	0	CH
62	H	H	A1	COOH	CH_2	J62	0	CH
63	H	H	A1	COOH	CH_2	J63	0	CH
64	H	H	A1	COOH	CH_2	J64	0	CH
65	H	H	A1	COOH	CH_2	J65	0	CH
66	H	H	A1	COOH	CH_2	J66	0	CH
67	H	H	A1	COOH	CH_2	J67	0	CH
68	H	H	A1	COOH	CH_2	J68	0	CH
69	H	H	A1	COOH	CH_2	J69	0	CH
70	H	H	A1	COOH	CH_2	J70	0	CH
71	H	H	A1	COOH	CH_2	J71	0	CH
72	H	H	A1	COOH	CH_2	J72	0	CH
73	H	H	A1	COOH	CH_2	J73	0	CH
74	H	H	A1	COOH	CH_2	J74	0	CH
75	H	H	A1	COOH	CH_2	J75	0	CH

Table 4

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
76	H	H	A1	COOH	CH_2	J76	0	CH
77	H	H	A1	COOH	CH_2	J77	0	CH
78	H	H	A1	COOH	CH_2	J78	0	CH
79	H	H	A1	COOH	CH_2	J79	0	CH
80	H	H	A1	COOH	CH_2	J80	0	CH
81	Me	Me	A1	COOH	CH_2	J1	0	CH
82	Me	Me	A1	COOH	CH_2	J2	0	CH
83	Me	Me	A1	COOH	CH_2	J3	0	CH
84	Me	Me	A1	COOH	CH_2	J4	0	CH
85	Me	Me	A1	COOH	CH_2	J5	0	CH
86	Me	Me	A1	COOH	CH_2	J6	0	CH
87	Me	Me	A1	COOH	CH_2	J7	0	CH
88	Me	Me	A1	COOH	CH_2	J8	0	CH
89	Me	Me	A1	COOH	CH_2	J9	0	CH
90	Me	Me	A1	COOH	CH_2	J10	0	CH
91	Me	Me	A1	COOH	CH_2	J11	0	CH
92	Me	Me	A1	COOH	CH_2	J12	0	CH
93	Me	Me	A1	COOH	CH_2	J13	0	CH
94	Me	Me	A1	COOH	CH_2	J14	0	CH
95	Me	Me	A1	COOH	CH_2	J15	0	CH
96	Me	Me	A1	COOH	CH_2	J16	0	CH
97	Me	Me	A1	COOH	CH_2	J17	0	CH
98	Me	Me	A1	COOH	CH_2	J18	0	CH
99	Me	Me	A1	COOH	CH_2	J19	0	CH
100	Me	Me	A1	COOH	CH_2	J20	0	CH

Table 5

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
101	Me	Me	A1	COOH	CH_2	J21	0	CH
102	Me	Me	A1	COOH	CH_2	J22	0	CH
103	Me	Me	A1	COOH	CH_2	J23	0	CH
104	Me	Me	A1	COOH	CH_2	J24	0	CH
105	Me	Me	A1	COOH	CH_2	J25	0	CH
106	Me	Me	A1	COOH	CH_2	J26	0	CH
107	Me	Me	A1	COOH	CH_2	J27	0	CH
108	Me	Me	A1	COOH	CH_2	J28	0	CH
109	Me	Me	A1	COOH	CH_2	J29	0	CH
110	Me	Me	A1	COOH	CH_2	J30	0	CH
111	Me	Me	A1	COOH	CH_2	J31	0	CH
112	Me	Me	A1	COOH	CH_2	J32	0	CH
113	Me	Me	A1	COOH	CH_2	J33	0	CH
114	Me	Me	A1	COOH	CH_2	J34	0	CH
115	Me	Me	A1	COOH	CH_2	J35	0	CH
116	Me	Me	A1	COOH	CH_2	J36	0	CH
117	Me	Me	A1	COOH	CH_2	J37	0	CH
118	Me	Me	A1	COOH	CH_2	J38	0	CH
119	Me	Me	A1	COOH	CH_2	J39	0	CH
120	Me	Me	A1	COOH	CH_2	J40	0	CH
121	Me	Me	A1	COOH	CH_2	J41	0	CH
122	Me	Me	A1	COOH	CH_2	J42	0	CH
123	Me	Me	A1	COOH	CH_2	J43	0	CH
124	Me	Me	A1	COOH	CH_2	J44	0	CH
125	Me	Me	A1	COOH	CH_2	J45	0	CH

Table 6

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
126	Me	Me	Al	COOH	CH_2	J46	0	CH
127	Me	Me	Al	COOH	CH_2	J47	0	CH
128	Me	Me	Al	COOH	CH_2	J48	0	CH
129	Me	Me	Al	COOH	CH_2	J49	0	CH
130	Me	Me	Al	COOH	CH_2	J50	0	CH
131	Me	Me	Al	COOH	CH_2	J51	0	CH
132	Me	Me	Al	COOH	CH_2	J52	0	CH
133	Me	Me	Al	COOH	CH_2	J53	0	CH
134	Me	Me	Al	COOH	CH_2	J54	0	CH
135	Me	Me	Al	COOH	CH_2	J55	0	CH
136	Me	Me	Al	COOH	CH_2	J56	0	CH
137	Me	Me	Al	COOH	CH_2	J57	0	CH
138	Me	Me	Al	COOH	CH_2	J58	0	CH
139	Me	Me	Al	COOH	CH_2	J59	0	CH
140	Me	Me	Al	COOH	CH_2	J60	0	CH
141	Me	Me	Al	COOH	CH_2	J61	0	CH
142	Me	Me	Al	COOH	CH_2	J62	0	CH
143	Me	Me	Al	COOH	CH_2	J63	0	CH
144	Me	Me	Al	COOH	CH_2	J64	0	CH
145	Me	Me	Al	COOH	CH_2	J65	0	CH
146	Me	Me	Al	COOH	CH_2	J66	0	CH
147	Me	Me	Al	COOH	CH_2	J67	0	CH
148	Me	Me	Al	COOH	CH_2	J68	0	CH
149	Me	Me	Al	COOH	CH_2	J69	0	CH
150	Me	Me	Al	COOH	CH_2	J70	0	CH

Table 7

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
151	Me	Me	Al	COOH	CH_2	J71	0	CH
152	Me	Me	Al	COOH	CH_2	J72	0	CH
153	Me	Me	Al	COOH	CH_2	J73	0	CH
154	Me	Me	Al	COOH	CH_2	J74	0	CH
155	Me	Me	Al	COOH	CH_2	J75	0	CH
156	Me	Me	Al	COOH	CH_2	J76	0	CH
157	Me	Me	Al	COOH	CH_2	J77	0	CH
158	Me	Me	Al	COOH	CH_2	J78	0	CH
159	Me	Me	Al	COOH	CH_2	J79	0	CH
160	Me	Me	Al	COOH	CH_2	J80	0	CH
161	Cl	Cl	Al	COOH	CH_2CH_2	J1	0	CH
162	Cl	Cl	Al	COOH	CH_2	J4	0	CH
163	Cl	Cl	Al	COOH	CH_2	J10	0	CH
164	Cl	Cl	Al	COOH	CH_2	J18	0	CH
165	Cl	Cl	Al	COOH	CH_2	J21	0	CH
166	Cl	Cl	Al	COOH	CH_2	J28	0	CH
167	Cl	Cl	Al	COOH	CH_2	J35	0	CH
168	Cl	Cl	Al	COOH	CH_2	J37	0	CH
169	Cl	Cl	Al	COOH	CH_2	J39	0	CH
170	Cl	Cl	Al	COOH	CH_2	J43	0	CH
171	Cl	Cl	Al	COOH	CH_2	J46	0	CH
172	Cl	Cl	Al	COOH	CH_2	J50	0	CH
173	Cl	Cl	Al	COOH	CH_2	J54	0	CH
174	Cl	Cl	Al	COOH	CH_2	J63	0	CH
175	Cl	Cl	Al	COOH	CH_2	J64	0	CH

Table 8

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
176	Cl	Cl	A1	COOH	CH_2	J65	0	CH
177	Cl	Cl	A1	COOH	CH_2	J66	0	CH
178	Cl	Cl	A1	COOH	CH_2	J67	0	CH
179	Cl	Cl	A1	COOH	CH_2	J71	0	CH
180	$-CH_2CH_2CH_2-$		A1	COOH	CH_2CH_2	J1	0	CH
181	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J4	0	CH
182	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J10	0	CH
183	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J18	0	CH
184	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J21	0	CH
185	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J28	0	CH
186	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J35	0	CH
187	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J37	0	CH
188	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J39	0	CH
189	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J43	0	CH
190	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J46	0	CH
191	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J50	0	CH
192	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J54	0	CH
193	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J63	0	CH
194	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J64	0	CH
195	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J65	0	CH
196	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J66	0	CH
197	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J67	0	CH
198	$-CH_2CH_2CH_2-$		A1	COOH	CH_2	J71	0	CH
199	$-OCH_2O-$		A1	COOH	CH_2CH_2	J1	0	CH
200	$-OCH_2O-$		A1	COOH	CH_2	J4	0	CH

Table 9

Compound No.	R^1 R^2	SCH_2-A	E	G	J	m	X
201	$-OCH_2O-$	A1	COOH	CH_2	J10	0	CH
202	$-OCH_2O-$	A1	COOH	CH_2	J18	0	CH
203	$-OCH_2O-$	A1	COOH	CH_2	J21	0	CH
204	$-OCH_2O-$	A1	COOH	CH_2	J28	0	CH
205	$-OCH_2O-$	A1	COOH	CH_2	J35	0	CH
206	$-OCH_2O-$	A1	COOH	CH_2	J37	0	CH
207	$-OCH_2O-$	A1	COOH	CH_2	J39	0	CH
208	$-OCH_2O-$	A1	COOH	CH_2	J43	0	CH
209	$-OCH_2O-$	A1	COOH	CH_2	J46	0	CH
210	$-OCH_2O-$	A1	COOH	CH_2	J50	0	CH
211	$-OCH_2O-$	A1	COOH	CH_2	J54	0	CH
212	$-OCH_2O-$	A1	COOH	CH_2	J63	0	CH
213	$-OCH_2O-$	A1	COOH	CH_2	J64	0	CH
214	$-OCH_2O-$	A1	COOH	CH_2	J65	0	CH
215	$-OCH_2O-$	A1	COOH	CH_2	J66	0	CH
216	$-OCH_2O-$	A1	COOH	CH_2	J67	0	CH
217	$-OCH_2O-$	A1	COOH	CH_2	J71	0	CH
218	$-OCH_2CH_2O-$	A1	COOH	CH_2CH_2	J1	0	CH
219	$-OCH_2CH_2O-$	A1	COOH	CH_2	J4	0	CH
220	$-OCH_2CH_2O-$	A1	COOH	CH_2	J10	0	CH
221	$-OCH_2CH_2O-$	A1	COOH	CH_2	J18	0	CH
222	$-OCH_2CH_2O-$	A1	COOH	CH_2	J35	0	CH
223	$-OCH_2CH_2O-$	A1	COOH	CH_2	J37	0	CH
224	$-OCH_2CH_2O-$	A1	COOH	CH_2	J39	0	CH
225	$-OCH_2CH_2O-$	A1	COOH	CH_2	J50	0	CH

Table 10

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
226	$-OCH_2CH_2O-$		A1	COOH	CH_2	J63	0	CH
227	$-OCH_2CH_2O-$		A1	COOH	CH_2	J64	0	CH
228	$-OCH_2CH_2O-$		A1	COOH	CH_2	J65	0	CH
229	$-OCH_2CH_2O-$		A1	COOH	CH_2	J67	0	CH
230	$-OCH_2CH_2O-$		A1	COOH	CH_2	J71	0	CH
231	OMe	OMe	A1	COOH	CH_2CH_2	J1	0	CH
232	OMe	OMe	A1	COOH	CH_2	J4	0	CH
233	OMe	OMe	A1	COOH	CH_2	J10	0	CH
234	OMe	OMe	A1	COOH	CH_2	J18	0	CH
235	OMe	OMe	A1	COOH	CH_2	J35	0	CH
236	OMe	OMe	A1	COOH	CH_2	J37	0	CH
237	OMe	OMe	A1	COOH	CH_2	J39	0	CH
238	OMe	OMe	A1	COOH	CH_2	J50	0	CH
239	OMe	OMe	A1	COOH	CH_2	J63	0	CH
240	OMe	OMe	A1	COOH	CH_2	J64	0	CH
241	OMe	OMe	A1	COOH	CH_2	J65	0	CH
242	OMe	OMe	A1	COOH	CH_2	J67	0	CH
243	OMe	OMe	A1	COOH	CH_2	J71	0	CH
244	F	F	A1	COOH	CH_2	J35	0	CH
245	F	F	A1	COOH	CH_2	J37	0	CH
246	F	F	A1	COOH	CH_2	J39	0	CH
247	F	F	A1	COOH	CH_2	J50	0	CH
248	F	F	A1	COOH	CH_2	J63	0	CH
249	F	F	A1	COOH	CH_2	J64	0	CH
250	F	F	A1	COOH	CH_2	J65	0	CH

Table 11

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
251	F	F	Al	COOH	CH_2	J67	0	CH
252	H	H	Al	COOH	CH_2	J35	0	N
253	H	H	Al	COOH	CH_2	J37	0	N
254	H	H	Al	COOH	CH_2	J39	0	N
255	H	H	Al	COOH	CH_2	J50	0	N
256	H	H	Al	COOH	CH_2	J63	0	N
257	H	H	Al	COOH	CH_2	J64	0	N
258	H	H	Al	COOH	CH_2	J65	0	N
259	H	H	Al	COOH	CH_2	J67	0	N
260	Me	H	Al	COOH	CH_2	J35	0	CH
261	Me	H	Al	COOH	CH_2	J37	0	CH
262	Me	H	Al	COOH	CH_2	J39	0	CH
263	Me	H	Al	COOH	CH_2	J50	0	CH
264	Me	H	Al	COOH	CH_2	J63	0	CH
265	Me	H	Al	COOH	CH_2	J64	0	CH
266	Me	H	Al	COOH	CH_2	J65	0	CH
267	Me	H	Al	COOH	CH_2	J67	0	CH
268	OMe	H	Al	COOH	CH_2	J35	0	CH
269	OMe	H	Al	COOH	CH_2	J37	0	CH
270	OMe	H	Al	COOH	CH_2	J39	0	CH
271	OMe	H	Al	COOH	CH_2	J50	0	CH
272	OMe	H	Al	COOH	CH_2	J63	0	CH
273	OMe	H	Al	COOH	CH_2	J64	0	CH
274	OMe	H	Al	COOH	CH_2	J65	0	CH
275	OMe	H	Al	COOH	CH_2	J67	0	CH

Table 12

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
276	OEt	H	A1	COOH	CH_2	J63	0	CH
277	OEt	H	A1	COOH	CH_2	J64	0	CH
278	OEt	H	A1	COOH	CH_2	J65	0	CH
279	CF3	H	A1	COOH	CH_2	J63	0	CH
280	CF3	H	A1	COOH	CH_2	J64	0	CH
281	CF3	H	A1	COOH	CH_2	J65	0	CH
282	CN	H	A1	COOH	CH_2	J63	0	CH
283	CN	H	A1	COOH	CH_2	J64	0	CH
284	CN	H	A1	COOH	CH_2	J65	0	CH
285	Cl	H	A1	COOH	CH_2	J63	0	N
286	Cl	H	A1	COOH	CH_2	J64	0	N
287	Cl	H	A1	COOH	CH_2	J65	0	N
288	Me	Me	A2	COOH	CH_2	J35	0	CH
289	Me	Me	A2	COOH	CH_2	J37	0	CH
290	Me	Me	A2	COOH	CH_2	J39	0	CH
291	Me	Me	A2	COOH	CH_2	J63	0	CH
292	Me	Me	A2	COOH	CH_2	J64	0	CH
293	Me	Me	A2	COOH	CH_2	J65	0	CH
294	Me	Me	A2	COOH	CH_2CH_2	J1	0	CH
295	Me	Me	A3	COOH	CH_2	J1	0	CH
296	Me	Me	A3	COOH	CH_2	J35	0	CH
297	Me	Me	A3	COOH	CH_2	J37	0	CH
298	Me	Me	A3	COOH	CH_2	J39	0	CH
299	Me	Me	A3	COOH	CH_2	J50	0	CH
300	Me	Me	A3	COOH	CH_2	J63	0	CH

Table 13

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
301	Me	Me	A3	COOH	CH_2	J64	0	CH
302	Me	Me	A3	COOH	CH_2	J65	0	CH
303	Me	Me	A3	COOH	CH_2	J67	0	CH
304	Me	Me	A3	COOH	CH_2CH_2	J1	0	CH
305	Me	Me	A3	COOH	CH_2CH_2	J63	0	CH
306	Me	Me	A4	COOH	CH_2	J1	0	CH
307	Me	Me	A4	COOH	CH_2	J35	0	CH
308	Me	Me	A4	COOH	CH_2	J37	0	CH
309	Me	Me	A4	COOH	CH_2	J39	0	CH
310	Me	Me	A4	COOH	CH_2	J50	0	CH
311	Me	Me	A4	COOH	CH_2	J63	0	CH
312	Me	Me	A4	COOH	CH_2	J64	0	CH
313	Me	Me	A4	COOH	CH_2	J65	0	CH
314	Me	Me	A4	COOH	CH_2	J67	0	CH
315	Me	Me	A4	COOH	CH_2CH_2	J1	0	CH
316	Me	Me	A4	COOH	CH_2CH_2	J63	0	CH
317	H	H	A4	COOH	CH_2	J37	0	CH
318	H	H	A4	COOH	CH_2	J39	0	CH
319	H	H	A4	COOH	CH_2	J63	0	CH
320	H	H	A4	COOH	CH_2	J64	0	CH
321	H	H	A4	COOH	CH_2	J65	0	CH
322	Cl	Cl	A4	COOH	CH_2	J37	0	CH
323	Cl	Cl	A4	COOH	CH_2	J39	0	CH
324	Cl	Cl	A4	COOH	CH_2	J63	0	CH
325	Cl	Cl	A4	COOH	CH_2	J64	0	CH

Table 14

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
326	Cl	Cl	A4	COOH	CH_2	J65	0	CH
327	H	H	A4	COOH	CH_2	J37	0	N
328	H	H	A4	COOH	CH_2	J39	0	N
329	H	H	A4	COOH	CH_2	J63	0	N
330	H	H	A4	COOH	CH_2	J64	0	N
331	H	H	A4	COOH	CH_2	J65	0	N
332	Me	Me	A5	COOH	CH_2	J1	0	CH
333	Me	Me	A5	COOH	CH_2CH_2	J1	0	CH
334	Me	Me	A6	COOH	CH_2	J1	0	CH
335	Me	Me	A6	COOH	CH_2CH_2	J1	0	CH
336	Me	Me	A7	COOH	CH_2	J1	0	CH
337	Me	Me	A7	COOH	CH_2CH_2	J1	0	CH
338	Me	Me	A8	COOH	CH_2	J1	0	CH
339	Me	Me	A8	COOH	CH_2CH_2	J1	0	CH
340	Me	Me	A9	COOH	CH_2	J1	0	CH
341	Me	Me	A9	COOH	CH_2CH_2	J1	0	CH
342	Me	Me	A10	COOH	CH_2	J1	0	CH
343	Me	Me	A10	COOH	CH_2CH_2	J1	0	CH
344	Me	Me	A11	COOH	CH_2	J37	0	CH
345	Me	Me	A11	COOH	CH_2	J39	0	CH
346	Me	Me	A11	COOH	CH_2	J50	0	CH
347	Me	Me	A11	COOH	CH_2	J63	0	CH
348	Me	Me	A11	COOH	CH_2	J64	0	CH
349	H	H	A11	COOH	CH_2	J37	0	CH
350	H	H	A11	COOH	CH_2	J39	0	CH

Table 15

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
351	H	H	A11	COOH	CH_2	J50	0	CH
352	H	H	A11	COOH	CH_2	J63	0	CH
353	H	H	A11	COOH	CH_2	J64	0	CH
354	H	H	A11	COOH	CH_2	J65	0	CH
355	Cl	Cl	A11	COOH	CH_2	J37	0	CH
356	Cl	Cl	A11	COOH	CH_2	J39	0	CH
357	Cl	Cl	A11	COOH	CH_2	J50	0	CH
358	Cl	Cl	A11	COOH	CH_2	J63	0	CH
359	Cl	Cl	A11	COOH	CH_2	J64	0	CH
360	Cl	Cl	A11	COOH	CH_2	J65	0	CH
361	H	H	A11	COOH	CH_2	J37	0	N
362	H	H	A11	COOH	CH_2	J39	0	N
363	H	H	A11	COOH	CH_2	J50	0	N
364	H	H	A11	COOH	CH_2	J63	0	N
365	H	H	A11	COOH	CH_2	J64	0	N
366	H	H	A11	COOH	CH_2	J65	0	N
367	Me	Me	A12	COOH	CH_2	J1	0	CH
368	Me	Me	A12	COOH	CH_2CH_2	J1	0	CH
369	Me	Me	A13	COOH	CH_2	J1	0	CH
370	Me	Me	A13	COOH	CH_2CH_2	J1	0	CH
371	Me	Me	A14	COOH	CH_2	J1	0	CH
372	Me	Me	A14	COOH	CH_2CH_2	J1	0	CH
373	Me	Me	A15	COOH	CH_2	J1	0	CH
374	Me	Me	A15	COOH	CH_2CH_2	J1	0	CH
375	Me	Me	A16	COOH	CH_2	J1	0	CH

Table 16

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
376	Me	Me	A16	COOH	CH_2CH_2	J1	0	CH
377	Me	Me	A16	COOH	CH_2	J37	0	CH
378	Me	Me	A16	COOH	CH_2	J39	0	CH
379	Me	Me	A16	COOH	CH_2	J50	0	CH
380	Me	Me	A16	COOH	CH_2	J63	0	CH
381	Me	Me	A16	COOH	CH_2	J64	0	CH
382	Me	Me	A16	COOH	CH_2	J65	0	CH
383	H	H	A16	COOH	CH_2	J37	0	CH
384	H	H	A16	COOH	CH_2	J39	0	CH
385	H	H	A16	COOH	CH_2	J50	0	CH
386	H	H	A16	COOH	CH_2	J63	0	CH
387	H	H	A16	COOH	CH_2	J64	0	CH
388	H	H	A16	COOH	CH_2	J65	0	CH
389	Me	Me	A17	COOH	CH_2	J1	0	CH
390	Me	Me	A17	COOH	CH_2CH_2	J1	0	CH
391	Me	Me	A18	COOH	CH_2CH_2	J1	0	CH
392	Me	Me	A18	COOH	CH_2	J37	0	CH
393	Me	Me	A18	COOH	CH_2	J39	0	CH
394	Me	Me	A18	COOH	CH_2	J50	0	CH
395	Me	Me	A18	COOH	CH_2	J63	0	CH
396	Me	Me	A18	COOH	CH_2	J64	0	CH
397	Me	Me	A18	COOH	CH_2	J65	0	CH
398	H	H	A18	COOH	CH_2	J37	0	CH
399	H	H	A18	COOH	CH_2	J39	0	CH
400	H	H	A18	COOH	CH_2	J50	0	CH

Table 17

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
401	H	H	A18	COOH	CH_2	J63	0	CH
402	H	H	A18	COOH	CH_2	J64	0	CH
403	H	H	A18	COOH	CH_2	J65	0	CH
404	Cl	Cl	A18	COOH	CH_2	J37	0	CH
405	Cl	Cl	A18	COOH	CH_2	J63	0	CH
406	Cl	Cl	A18	COOH	CH_2	J64	0	CH
407	Cl	Cl	A18	COOH	CH_2	J65	0	CH
408	H	H	A18	COOH	CH_2	J37	0	N
409	H	H	A18	COOH	CH_2	J39	0	N
410	H	H	A18	COOH	CH_2	J63	0	N
411	H	H	A18	COOH	CH_2	J64	0	N
412	H	H	A18	COOH	CH_2	J65	0	N
413	Me	H	A18	COOH	CH_2	J37	0	CH
414	Me	H	A18	COOH	CH_2	J39	0	CH
415	Me	H	A18	COOH	CH_2	J63	0	CH
416	Me	H	A18	COOH	CH_2	J64	0	CH
417	Me	H	A18	COOH	CH_2	J65	0	CH
418	OMe	H	A18	COOH	CH_2	J37	0	CH
419	OMe	H	A18	COOH	CH_2	J39	0	CH
420	OMe	H	A18	COOH	CH_2	J63	0	CH
421	OMe	H	A18	COOH	CH_2	J64	0	CH
422	OMe	H	A18	COOH	CH_2	J65	0	CH
423	OEt	H	A18	COOH	CH_2	J63	0	CH
424	OEt	H	A18	COOH	CH_2	J64	0	CH
425	OEt	H	A18	COOH	CH_2	J65	0	CH

Table 18

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
426	CF3	H	A18	COOH	CH_2	J63	0	CH
427	CF3	H	A18	COOH	CH_2	J64	0	CH
428	CF3	H	A18	COOH	CH_2	J65	0	CH
429	CN	H	A18	COOH	CH_2	J63	0	CH
430	CN	H	A18	COOH	CH_2	J64	0	CH
431	CN	H	A18	COOH	CH_2	J65	0	CH
432	F	H	A18	COOH	CH_2	J63	0	CH
433	F	H	A18	COOH	CH_2	J64	0	CH
434	F	H	A18	COOH	CH_2	J65	0	CH
435	Cl	H	A18	COOH	CH_2	J63	0	N
436	Cl	H	A18	COOH	CH_2	J64	0	N
437	Cl	H	A18	COOH	CH_2	J65	0	N
438	H	H	A18	COOH	CH_2	J37	0	N
439	Me	Me	A19	COOH	CH_2	J1	0	CH
440	Me	Me	A19	COOH	CH_2CH_2	J1	0	CH
441	Me	Me	A19	COOH	CH_2	J37	0	CH
442	Me	Me	A19	COOH	CH_2	J39	0	CH
443	Me	Me	A19	COOH	CH_2	J50	0	CH
444	Me	Me	A19	COOH	CH_2	J63	0	CH
445	Me	Me	A19	COOH	CH_2	J64	0	CH
446	Me	Me	A19	COOH	CH_2	J65	0	CH
447	H	H	A19	COOH	CH_2	J1	0	CH
448	H	H	A19	COOH	CH_2CH_2	J1	0	CH
449	H	H	A19	COOH	CH_2	J37	0	CH
450	H	H	A19	COOH	CH_2	J39	0	CH

Table 19

Compound No.	R'	R²	SCH_2-A	E	G	J	m	X.
451	H	H	A19	COOH	CH_2	J50	0	CH
452	H	H	A19	COOH	CH_2	J63	0	CH
453	H	H	A19	COOH	CH_2	J64	0	CH
454	H	H	A19	COOH	CH_2	J65	0	CH
455	Me	Me	A20	COOH	CH_2	J64	0	CH
456	Me	Me	A20	COOH	CH_2	J65	0	CH
457	Me	Me	A20	COOH	CH_2	J67	0	CH
458	Me	Me	A20	COOH	CH_2	J71	0	CH
459	H	H	A20	COOH	CH_2	J64	0	CH
460	H	H	A20	COOH	CH_2	J65	0	CH
461	H	H	A20	COOH	CH_2	J67	0	CH
462	H	H	A20	COOH	CH_2	J71	0	CH
463	Cl	Cl	A20	COOH	CH_2	J64	0	CH
464	Cl	Cl	A20	COOH	CH_2	J65	0	CH
465	Cl	Cl	A20	COOH	CH_2	J67	0	CH
466	Cl	Cl	A20	COOH	CH_2	J71	0	CH
467	H	H	A20	COOH	CH_2	J64	0	N
468	H	H	A20	COOH	CH_2	J65	0	N
469	H	H	A20	COOH	CH_2	J67	0	N
470	H	H	A20	COOH	CH_2	J71	0	N
471	Me	H	A20	COOH	CH_2	J64	0	CH
472	Me	H	A20	COOH	CH_2	J65	0	CH
473	Me	H	A20	COOH	CH_2	J67	0	CH
474	Me	H	A20	COOH	CH_2	J71	0	CH
475	OMe	H	A20	COOH	CH_2	J64	0	CH

Table 20

Compound No.	R'	R²	SCH_2-A	E	G	J	m	X
476	OMe	H	A20	COOH	CH_2	J65	0	CH
477	OMe	H	A20	COOH	CH_2	J67	0	CH
478	OMe	H	A20	COOH	CH_2	J71	0	CH
479	OEt	H	A20	COOH	CH_2	J64	0	CH
480	OEt	H	A20	COOH	CH_2	J65	0	CH
481	OEt	H	A20	COOH	CH_2	J67	0	CH
482	OEt	H	A20	COOH	CH_2	J71	0	CH
483	F	H	A20	COOH	CH_2	J64	0	CH
484	F	H	A20	COOH	CH_2	J65	0	CH
485	F	H	A20	COOH	CH_2	J67	0	CH
486	F	H	A20	COOH	CH_2	J71	0	CH
487	CF3	H	A20	COOH	CH_2	J64	0	CH
488	CF3	H	A20	COOH	CH_2	J65	0	CH
489	CF3	H	A20	COOH	CH_2	J67	0	CH
490	CF3	H	A20	COOH	CH_2	J71	0	CH
491	CN	H	A20	COOH	CH_2	J64	0	CH
492	CN	H	A20	COOH	CH_2	J65	0	CH
493	CN	H	A20	COOH	CH_2	J67	0	CH
494	CN	H	A20	COOH	CH_2	J71	0	CH
495	Cl	H	A20	COOH	CH_2	J64	0	N
496	Cl	H	A20	COOH	CH_2	J65	0	N
497	Cl	H	A20	COOH	CH_2	J67	0	N
498	Cl	H	A20	COOH	CH_2	J71	0	N
499	H	H	A21	COOH	CH_2	J63	0	CH
500	H	H	A21	COOH	CH_2	J65	0	CH

Table 21

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
501	Me	Me	A1	COOH	CH_2CH_2	J1	0	CH
502	Me	Me	A1	COOH	CH_2CH_2	J37	0	CH
503	Me	Me	A1	COOH	CH_2CH_2	J39	0	CH
504	Me	Me	A1	COOH	CH_2CH_2	J50	0	CH
505	Me	Me	A1	COOH	CH_2CH_2	J62	0	CH
506	Me	Me	A1	COOH	CH_2CH_2	J63	0	CH
507	Me	Me	A1	COOH	CH_2CH_2	J64	0	CH
508	Me	Me	A1	COOH	CH_2CH_2	J65	0	CH
509	H	H	A1	COOH	CH_2CH_2	J1	0	CH
510	H	H	A1	COOH	CH_2CH_2	J37	0	CH
511	H	H	A1	COOH	CH_2CH_2	J39	0	CH
512	H	H	A1	COOH	CH_2CH_2	J50	0	CH
513	H	H	A1	COOH	CH_2CH_2	J62	0	CH
514	H	H	A1	COOH	CH_2CH_2	J63	0	CH
515	H	H	A1	COOH	CH_2CH_2	J64	0	CH
516	H	H	A1	COOH	CH_2CH_2	J65	0	CH
517	Me	Me	A4	COOH	CH_2CH_2	J37	0	CH
518	Me	Me	A4	COOH	CH_2CH_2	J39	0	CH
519	Me	Me	A4	COOH	CH_2CH_2	J67	0	CH
520	Me	Me	A4	COOH	CH_2CH_2	J64	0	CH
521	Me	Me	A4	COOH	CH_2CH_2	J65	0	CH
522	H	H	A4	COOH	CH_2CH_2	J37	0	CH
523	H	H	A4	COOH	CH_2CH_2	J39	0	CH
524	H	H	A4	COOH	CH_2CH_2	J63	0	CH
525	H	H	A4	COOH	CH_2CH_2	J64	0	CH

Table 22

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
526	H	H	A4	COOH	CH_2CH_2	J65	0	CH
527	H	H	A11	COOH	CH_2CH_2	J37	0	CH
528	H	H	A11	COOH	CH_2CH_2	J39	0	CH
529	H	H	A11	COOH	CH_2CH_2	J63	0	CH
530	H	H	A11	COOH	CH_2CH_2	J64	0	CH
531	H	H	A11	COOH	CH_2CH_2	J65	0	CH
532	H	H	A18	COOH	CH_2CH_2	J37	0	CH
533	H	H	A18	COOH	CH_2CH_2	J39	0	CH
534	H	H	A18	COOH	CH_2CH_2	J63	0	CH
535	H	H	A18	COOH	CH_2CH_2	J64	0	CH
536	H	H	A18	COOH	CH_2CH_2	J65	0	CH
537	Me	Me	A20	COOH	CH_2CH_2	J37	0	CH
538	Me	Me	A20	COOH	CH_2CH_2	J39	0	CH
539	Me	Me	A20	COOH	CH_2CH_2	J63	0	CH
540	Me	Me	A20	COOH	CH_2CH_2	J64	0	CH
541	Me	Me	A20	COOH	CH_2CH_2	J65	0	CH
542	H	H	A20	COOH	CH_2CH_2	J37	0	CH
543	H	H	A20	COOH	CH_2CH_2	J39	0	CH
544	H	H	A20	COOH	CH_2CH_2	J63	0	CH
545	H	H	A20	COOH	CH_2CH_2	J64	0	CH
546	H	H	A20	COOH	CH_2CH_2	J65	0	CH
547	Me	Me	A1	COOH	CO	J1	0	CH
548	Me	Me	A1	COOH	CO	J63	0	CH
549	H	H	A1	COOH	CO	J1	0	CH
550	H	H	A1	COOH	CO	J63	0	CH

Table 23

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
551	Me	Me	A4	COOH	CO	J1	0	CH
552	Me	Me	A4	COOH	CO	J63	0	CH
553	H	H	A4	COOH	CO	J1	0	CH
554	H	H	A4	COOH	CO	J63	0	CH
555	H	H	A11	COOH	CO	J1	0	CH
556	H	H	A11	COOH	CO	J63	0	CH
557	H	H	A18	COOH	CO	J1	0	CH
558	H	H	A18	COOH	CO	J63	0	CH
559	H	H	A20	COOH	CO	J1	0	CH
560	H	H	A20	COOH	CO	J63	0	CH
561	Me	Me	A1	COOH	SO_2	J1	0	CH
562	Me	Me	A1	COOH	SO_2	J63	0	CH
563	H	H	A1	COOH	SO_2	J1	0	CH
564	H	H	A1	COOH	SO_2	J63	0	CH
565	H	H	A4	COOH	SO_2	J1	0	CH
566	H	H	A4	COOH	SO_2	J63	0	CH
567	H	H	A11	COOH	SO_2	J1	0	CH
568	H	H	A11	COOH	SO_2	J63	0	CH
569	H	H	A18	COOH	SO_2	J1	0	CH
570	H	H	A18	COOH	SO_2	J63	0	CH
571	H	H	A20	COOH	SO_2	J1	0	CH
572	H	H	A20	COOH	SO_2	J63	0	CH
573	H	H	A1	COOH	CH_2CO	J1	0	CH
574	H	H	A1	COOH	CH_2CO	J2	0	CH
575	H	H	A1	COOH	CH_2CO	J3	0	CH

Table 24

Compound No.	R'	R'	SCH_2-A	E	G	J	m	X
576	H	H	A1	COOH	CH_2CO	J4	0	CH
577	H	H	A1	COOH	CH_2CO	J5	0	CH
578	H	H	A1	COOH	CH_2CO	J6	0	CH
579	H	H	A1	COOH	CH_2CO	J7	0	CH
580	H	H	A1	COOH	CH_2CO	J8	0	CH
581	H	H	A1	COOH	CH_2CO	J9	0	CH
582	H	H	A1	COOH	CH_2CO	J10	0	CH
583	H	H	A1	COOH	CH_2CO	J11	0	CH
584	H	H	A1	COOH	CH_2CO	J12	0	CH
585	H	H	A1	COOH	CH_2CO	J13	0	CH
586	H	H	A1	COOH	CH_2CO	J17	0	CH
587	H	H	A1	COOH	CH_2CO	J18	0	CH
588	H	H	A1	COOH	CH_2CO	J19	0	CH
589	H	H	A1	COOH	CH_2CO	J23	0	CH
590	H	H	A1	COOH	CH_2CO	J24	0	CH
591	H	H	A1	COOH	CH_2CO	J25	0	CH
592	H	H	A1	COOH	CH_2CO	J36	0	CH
593	H	H	A1	COOH	CH_2CO	J47	0	CH
594	H	H	A1	COOH	CH_2CO	J57	0	CH
595	H	H	A1	COOH	CH_2CO	J62	0	CH
596	Me	Me	A1	COOH	CH_2CO	J1	0	CH
597	Me	Me	A1	COOH	CH_2CO	J2	0	CH
598	Me	Me	A1	COOH	CH_2CO	J3	0	CH
599	Me	Me	A1	COOH	CH_2CO	J4	0	CH
600	Me	Me	A1	COOH	CH_2CO	J5	0	CH

Table 25

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
601	Me	Me	A1	COOH	CH_2CO	J6	0	CH
602	Me	Me	A1	COOH	CH_2CO	J7	0	CH
603	Me	Me	A1	COOH	CH_2CO	J8	0	CH
604	Me	Me	A1	COOH	CH_2CO	J9	0	CH
605	Me	Me	A1	COOH	CH_2CO	J10	0	CH
606	Me	Me	A1	COOH	CH_2CO	J11	0	CH
607	Me	Me	A1	COOH	CH_2CO	J12	0	CH
608	Me	Me	A1	COOH	CH_2CO	J13	0	CH
609	Me	Me	A1	COOH	CH_2CO	J17	0	CH
610	Me	Me	A1	COOH	CH_2CO	J18	0	CH
611	Me	Me	A1	COOH	CH_2CO	J19	0	CH
612	Me	Me	A1	COOH	CH_2CO	J23	0	CH
613	Me	Me	A1	COOH	CH_2CO	J24	0	CH
614	Me	Me	A1	COOH	CH_2CO	J25	0	CH
615	Me	Me	A1	COOH	CH_2CO	J36	0	CH
616	Me	Me	A1	COOH	CH_2CO	J47	0	CH
617	Me	Me	A1	COOH	CH_2CO	J57	0	CH
618	Me	Me	A1	COOH	CH_2CO	J62	0	CH
619	H	H	A1	COOH	CH_2CONH	J1	0	CH
620	H	H	A1	COOH	CH_2CONH	J2	0	CH
621	H	H	A1	COOH	CH_2CONH	J3	0	CH
622	H	H	A1	COOH	CH_2CONH	J4	0	CH
623	H	H	A1	COOH	CH_2CONH	J5	0	CH
624	H	H	A1	COOH	CH_2CONH	J6	0	CH
625	H	H	A1	COOH	CH_2CONH	J7	0	CH

Table 26

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
626	H	H	A1	COOH	CH_2CONH	J8	0	CH
627	H	H	A1	COOH	CH_2CONH	J9	0	CH
628	H	H	A1	COOH	CH_2CONH	J10	0	CH
629	H	H	A1	COOH	CH_2CONH	J11	0	CH
630	H	H	A1	COOH	CH_2CONH	J12	0	CH
631	H	H	A1	COOH	CH_2CONH	J13	0	CH
632	H	H	A1	COOH	CH_2CONH	J14	0	CH
633	H	H	A1	COOH	CH_2CONH	J15	0	CH
634	H	H	A1	COOH	CH_2CONH	J16	0	CH
635	H	H	A1	COOH	CH_2CONH	J17	0	CH
636	H	H	A1	COOH	CH_2CONH	J18	0	CH
637	H	H	A1	COOH	CH_2CONH	J19	0	CH
638	H	H	A1	COOH	CH_2CONH	J20	0	CH
639	H	H	A1	COOH	CH_2CONH	J21	0	CH
640	H	H	A1	COOH	CH_2CONH	J22	0	CH
641	H	H	A1	COOH	CH_2CONH	J23	0	CH
642	H	H	A1	COOH	CH_2CONH	J24	0	CH
643	H	H	A1	COOH	CH_2CONH	J25	0	CH
644	H	H	A1	COOH	CH_2CONH	J26	0	CH
645	H	H	A1	COOH	CH_2CONH	J27	0	CH
646	H	H	A1	COOH	CH_2CONH	J28	0	CH
647	H	H	A1	COOH	CH_2CONH	J29	0	CH
648	H	H	A1	COOH	CH_2CONH	J30	0	CH
649	H	H	A1	COOH	CH_2CONH	J31	0	CH
650	H	H	A1	COOH	CH_2CONH	J32	0	CH

Table 27

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
651	H	H	A1	COOH	CH_2CONH	J33	0	CH
652	H	H	A1	COOH	CH_2CONH	J34	0	CH
653	H	H	A1	COOH	CH_2CONH	J35	0	CH
654	H	H	A1	COOH	CH_2CONH	J37	0	CH
655	H	H	A1	COOH	CH_2CONH	J39	0	CH
656	H	H	A1	COOH	CH_2CONH	J62	0	CH
657	H	H	A1	COOH	CH_2CONH	J63	0	CH
658	Me	Me	A1	COOH	CH_2CONH	J1	0	CH
659	Me	Me	A1	COOH	CH_2CONH	J2	0	CH
660	Me	Me	A1	COOH	CH_2CONH	J3	0	CH
661	Me	Me	A1	COOH	CH_2CONH	J4	0	CH
662	Me	Me	A1	COOH	CH_2CONH	J5	0	CH
663	Me	Me	A1	COOH	CH_2CONH	J6	0	CH
664	Me	Me	A1	COOH	CH_2CONH	J7	0	CH
665	Me	Me	A1	COOH	CH_2CONH	J8	0	CH
666	Me	Me	A1	COOH	CH_2CONH	J9	0	CH
667	Me	Me	A1	COOH	CH_2CONH	J10	0	CH
668	Me	Me	A1	COOH	CH_2CONH	J11	0	CH
669	Me	Me	A1	COOH	CH_2CONH	J12	0	CH
670	Me	Me	A1	COOH	CH_2CONH	J13	0	CH
671	Me	Me	A1	COOH	CH_2CONH	J14	0	CH
672	Me	Me	A1	COOH	CH_2CONH	J15	0	CH
673	Me	Me	A1	COOH	CH_2CONH	J16	0	CH
674	Me	Me	A1	COOH	CH_2CONH	J17	0	CH
675	Me	Me	A1	COOH	CH_2CONH	J18	0	CH

Table 28

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
676	Me	Me	Al	COOH	CH_2CONH	J19	0	CH
677	Me	Me	Al	COOH	CH_2CONH	J20	0	CH
678	Me	Me	Al	COOH	CH_2CONH	J21	0	CH
679	Me	Me	Al	COOH	CH_2CONH	J22	0	CH
680	Me	Me	Al	COOH	CH_2CONH	J23	0	CH
681	Me	Me	Al	COOH	CH_2CONH	J24	0	CH
682	Me	Me	Al	COOH	CH_2CONH	J25	0	CH
683	Me	Me	Al	COOH	CH_2CONH	J26	0	CH
684	Me	Me	Al	COOH	CH_2CONH	J27	0	CH
685	Me	Me	Al	COOH	CH_2CONH	J28	0	CH
686	Me	Me	Al	COOH	CH_2CONH	J29	0	CH
687	Me	Me	Al	COOH	CH_2CONH	J30	0	CH
688	Me	Me	Al	COOH	CH_2CONH	J31	0	CH
689	Me	Me	Al	COOH	CH_2CONH	J32	0	CH
690	Me	Me	Al	COOH	CH_2CONH	J33	0	CH
691	Me	Me	Al	COOH	CH_2CONH	J34	0	CH
692	Me	Me	Al	COOH	CH_2CONH	J35	0	CH
693	Me	Me	Al	COOH	CH_2CONH	J37	0	CH
694	Me	Me	Al	COOH	CH_2CONH	J39	0	CH
695	Me	Me	Al	COOH	CH_2CONH	J62	0	CH
696	Me	Me	Al	COOH	CH_2CONH	J63	0	CH
697	H	H	Al	COOH	CH_2CH_2O	J1	0	CH
698	H	H	Al	COOH	CH_2CH_2O	J2	0	CH
699	H	H	Al	COOH	CH_2CH_2O	J3	0	CH
700	H	H	Al	COOH	CH_2CH_2O	J4	0	CH

Table 29

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
701	H	H	A1	COOH	CH_2CH_2O	J5	0	CH
702	H	H	A1	COOH	CH_2CH_2O	J6	0	CH
703	H	H	A1	COOH	CH_2CH_2O	J7	0	CH
704	H	H	A1	COOH	CH_2CH_2O	J8	0	CH
705	H	H	A1	COOH	CH_2CH_2O	J9	0	CH
706	H	H	A1	COOH	CH_2CH_2O	J10	0	CH
707	H	H	A1	COOH	CH_2CH_2O	J11	0	CH
708	H	H	A1	COOH	CH_2CH_2O	J12	0	CH
709	H	H	A1	COOH	CH_2CH_2O	J13	0	CH
710	H	H	A1	COOH	CH_2CH_2O	J14	0	CH
711	H	H	A1	COOH	CH_2CH_2O	J15	0	CH
712	H	H	A1	COOH	CH_2CH_2O	J16	0	CH
713	H	H	A1	COOH	CH_2CH_2O	J17	0	CH
714	H	H	A1	COOH	CH_2CH_2O	J18	0	CH
715	H	H	A1	COOH	CH_2CH_2O	J19	0	CH
716	H	H	A1	COOH	CH_2CH_2O	J20	0	CH
717	H	H	A1	COOH	CH_2CH_2O	J21	0	CH
718	H	H	A1	COOH	CH_2CH_2O	J22	0	CH
719	H	H	A1	COOH	CH_2CH_2O	J23	0	CH
720	H	H	A1	COOH	CH_2CH_2O	J24	0	CH
721	H	H	A1	COOH	CH_2CH_2O	J25	0	CH
722	H	H	A1	COOH	CH_2CH_2O	J26	0	CH
723	H	H	A1	COOH	CH_2CH_2O	J27	0	CH
724	H	H	A1	COOH	CH_2CH_2O	J28	0	CH
725	H	H	A1	COOH	CH_2CH_2O	J29	0	CH

Table 30

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
726	H	H	A1	COOH	CH_2CH_2O	J30	0	CH
727	H	H	A1	COOH	CH_2CH_2O	J31	0	CH
728	H	H	A1	COOH	CH_2CH_2O	J32	0	CH
729	H	H	A1	COOH	CH_2CH_2O	J33	0	CH
730	H	H	A1	COOH	CH_2CH_2O	J34	0	CH
731	H	H	A1	COOH	CH_2CH_2O	J35	0	CH
732	H	H	A1	COOH	CH_2CH_2O	J37	0	CH
733	H	H	A1	COOH	CH_2CH_2O	J39	0	CH
734	H	H	A1	COOH	CH_2CH_2O	J62	0	CH
735	H	H	A1	COOH	CH_2CH_2O	J63	0	CH
736	Me	Me	A1	COOH	CH_2CH_2O	J1	0	CH
737	Me	Me	A1	COOH	CH_2CH_2O	J2	0	CH
738	Me	Me	A1	COOH	CH_2CH_2O	J3	0	CH
739	Me	Me	A1	COOH	CH_2CH_2O	J4	0	CH
740	Me	Me	A1	COOH	CH_2CH_2O	J5	0	CH
741	Me	Me	A1	COOH	CH_2CH_2O	J6	0	CH
742	Me	Me	A1	COOH	CH_2CH_2O	J7	0	CH
743	Me	Me	A1	COOH	CH_2CH_2O	J8	0	CH
744	Me	Me	A1	COOH	CH_2CH_2O	J9	0	CH
745	Me	Me	A1	COOH	CH_2CH_2O	J10	0	CH
746	Me	Me	A1	COOH	CH_2CH_2O	J11	0	CH
747	Me	Me	A1	COOH	CH_2CH_2O	J12	0	CH
748	Me	Me	A1	COOH	CH_2CH_2O	J13	0	CH
749	Me	Me	A1	COOH	CH_2CH_2O	J14	0	CH
750	Me	Me	A1	COOH	CH_2CH_2O	J15	0	CH

Table 31

Compound No.	R^1	R^4	SCH_2-A	E	G	J	m	X
751	Me	Me	Al	COOH	CH_2CH_2O	J15	0	CH
752	Me	Me	Al	COOH	CH_2CH_2O	J16	0	CH
753	Me	Me	Al	COOH	CH_2CH_2O	J17	0	CH
754	Me	Me	Al	COOH	CH_2CH_2O	J18	0	CH
755	Me	Me	Al	COOH	CH_2CH_2O	J19	0	CH
756	Me	Me	Al	COOH	CH_2CH_2O	J20	0	CH
757	Me	Me	Al	COOH	CH_2CH_2O	J21	0	CH
758	Me	Me	Al	COOH	CH_2CH_2O	J22	0	CH
759	Me	Me	Al	COOH	CH_2CH_2O	J23	0	CH
760	Me	Me	Al	COOH	CH_2CH_2O	J24	0	CH
761	Me	Me	Al	COOH	CH_2CH_2O	J25	0	CH
762	Me	Me	Al	COOH	CH_2CH_2O	J26	0	CH
763	Me	Me	Al	COOH	CH_2CH_2O	J27	0	CH
764	Me	Me	Al	COOH	CH_2CH_2O	J28	0	CH
765	Me	Me	Al	COOH	CH_2CH_2O	J29	0	CH
766	Me	Me	Al	COOH	CH_2CH_2O	J30	0	CH
767	Me	Me	Al	COOH	CH_2CH_2O	J31	0	CH
768	Me	Me	Al	COOH	CH_2CH_2O	J32	0	CH
769	Me	Me	Al	COOH	CH_2CH_2O	J33	0	CH
770	Me	Me	Al	COOH	CH_2CH_2O	J34	0	CH
771	Me	Me	Al	COOH	CH_2CH_2O	J35	0	CH
772	Me	Me	Al	COOH	CH_2CH_2O	J37	0	CH
773	Me	Me	Al	COOH	CH_2CH_2O	J39	0	CH
774	Me	Me	Al	COOH	CH_2CH_2O	J62	0	CH
775	Me	Me	Al	COOH	CH_2CH_2O	J63	0	CH

Table 32

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
776	H	H	A1	COOH	CH_2S	J1	0	CH
777	H	H	A1	COOH	CH_2S	J2	0	CH
778	H	H	A1	COOH	CH_2S	J3	0	CH
779	H	H	A1	COOH	CH_2S	J4	0	CH
780	H	H	A1	COOH	CH_2S	J8	0	CH
781	H	H	A1	COOH	CH_2S	J9	0	CH
782	H	H	A1	COOH	CH_2S	J10	0	CH
783	Me	Me	A1	COOH	CH_2S	J1	0	CH
784	Me	Me	A1	COOH	CH_2S	J2	0	CH
785	Me	Me	A1	COOH	CH_2S	J3	0	CH
786	Me	Me	A1	COOH	CH_2S	J4	0	CH
787	Me	Me	A1	COOH	CH_2S	J8	0	CH
788	Me	Me	A1	COOH	CH_2S	J9	0	CH
789	Me	Me	A1	COOH	CH_2S	J10	0	CH
790	H	H	A1	COOH	CH_2SO_2	J1	0	CH
791	H	H	A1	COOH	CH_2SO_2	J2	0	CH
792	H	H	A1	COOH	CH_2SO_2	J3	0	CH
793	H	H	A1	COOH	CH_2SO_2	J4	0	CH
794	H	H	A1	COOH	CH_2SO_2	J8	0	CH
795	H	H	A1	COOH	CH_2SO_2	J9	0	CH
796	H	H	A1	COOH	CH_2SO_2	J10	0	CH
797	Me	Me	A1	COOH	CH_2SO_2	J1	0	CH
798	Me	Me	A1	COOH	CH_2SO_2	J2	0	CH
799	Me	Me	A1	COOH	CH_2SO_2	J3	0	CH
800	Me	Me	A1	COOH	CH_2SO_2	J4	0	CH

Table 33

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
801	Me	Me	A1	COOH	CH_2SO_2	J8	0	CH
802	Me	Me	A1	COOH	CH_2SO_2	J9	0	CH
803	Me	Me	A1	COOH	CH_2SO_2	J10	0	CH
804	Me	Me	A1	COOH	CH_2	J81	0	CH
805	Me	Me	A1	COOH	CH_2	J82	0	CH
806	Me	Me	A1	COOH	CH_2	J83	0	CH
807	Me	Me	A1	COOH	CH_2	J84	0	CH
808	Me	Me	A1	COOH	CH_2	J85	0	CH
809	H	H	A1	COOH	CH_2	J81	0	CH
810	H	H	A1	COOH	CH_2	J82	0	CH
811	H	H	A1	COOH	CH_2	J83	0	CH
812	H	H	A1	COOH	CH_2	J84	0	CH
813	H	H	A1	COOH	CH_2	J85	0	CH
814	Me	Me	A1	COOH	CH_2CH_2	J1	1	CH
815	Me	Me	A1	COOH	CH_2	J1	1	CH
816	Me	Me	A1	COOH	CH_2	J37	1	CH
817	Me	Me	A1	COOH	CH_2	J39	1	CH
818	Me	Me	A1	COOH	CH_2	J50	1	CH
819	Me	Me	A1	COOH	CH_2	J63	1	CH
820	Me	Me	A1	COOH	CH_2	J64	1	CH
821	Me	Me	A1	COOH	CH_2	J65	1	CH
822	H	H	A1	COOH	CH_2	J37	1	CH
823	H	H	A1	COOH	CH_2	J39	1	CH
824	H	H	A1	COOH	CH_2	J50	1	CH
825	H	H	A1	COOH	CH_2	J63	1	CH

Table 35

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
851	H	H	A18	COOH	CH_2	J65	1	CH
852	H	H	A20	COOH	CH_2	J37	1	CH
853	H	H	A20	COOH	CH_2	J39	1	CH
854	H	H	A20	COOH	CH_2	J50	1	CH
855	H	H	A20	COOH	CH_2	J63	1	CH
856	H	H	A20	COOH	CH_2	J64	1	CH
857	H	H	A20	COOH	CH_2	J65	1	CH
858	Me	Me	A1	COOH	CH_2CH_2	J1	2	CH
859	Me	Me	A1	COOH	CH_2	J1	2	CH
860	Me	Me	A1	COOH	CH_2	J37	2	CH
861	Me	Me	A1	COOH	CH_2	J39	2	CH
862	Me	Me	A1	COOH	CH_2	J50	2	CH
863	Me	Me	A1	COOH	CH_2	J63	2	CH
864	Me	Me	A1	COOH	CH_2	J64	2	CH
865	Me	Me	A1	COOH	CH_2	J65	2	CH
866	H	H	A1	COOH	CH_2	J37	2	CH
867	H	H	A1	COOH	CH_2	J39	2	CH
868	H	H	A1	COOH	CH_2	J50	2	CH
869	H	H	A1	COOH	CH_2	J63	2	CH
870	H	H	A1	COOH	CH_2	J64	2	CH
871	H	H	A1	COOH	CH_2	J65	2	CH
872	Cl	Cl	A1	COOH	CH_2	J37	2	CH
873	Cl	Cl	A1	COOH	CH_2	J39	2	CH
874	Cl	Cl	A1	COOH	CH_2	J50	2	CH
875	Cl	Cl	A1	COOH	CH_2	J63	2	CH

Table 36

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
876	Cl	Cl	A1	COOH	CH_2	J64	2	CH
877	Cl	Cl	A1	COOH	CH_2	J65	2	CH
878	H	H	A1	COOH	CH_2	J37	2	N
879	H	H	A1	COOH	CH_2	J39	2	N
880	H	H	A1	COOH	CH_2	J50	2	N
881	H	H	A1	COOH	CH_2	J63	2	N
882	H	H	A1	COOH	CH_2	J64	2	N
883	H	H	A1	COOH	CH_2	J65	2	N
884	Me	H	A1	COOH	CH_2	J37	2	CH
885	Me	H	A1	COOH	CH_2	J63	2	CH
886	Me	H	A1	COOH	CH_2	J64	2	CH
887	Me	H	A1	COOH	CH_2	J65	2	CH
888	H	H	A4	COOH	CH_2	J37	2	CH
889	H	H	A4	COOH	CH_2	J63	2	CH
890	H	H	A4	COOH	CH_2	J64	2	CH
891	H	H	A4	COOH	CH_2	J65	2	CH
892	Me	Me	A4	COOH	CH_2	J37	2	CH
893	Me	Me	A4	COOH	CH_2	J63	2	CH
894	Me	Me	A4	COOH	CH_2	J64	2	CH
895	Me	Me	A4	COOH	CH_2	J65	2	CH
896	Cl	Cl	A4	COOH	CH_2	J37	2	CH
897	Cl	Cl	A4	COOH	CH_2	J63	2	CH
898	Cl	Cl	A4	COOH	CH_2	J64	2	CH
899	Cl	Cl	A4	COOH	CH_2	J65	2	CH
900	H	H	A4	COOH	CH_2	J37	2	N

Table 37

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
901	H	H	A4	COOH	CH_2	J63	2	N
902	H	H	A4	COOH	CH_2	J64	2	N
903	H	H	A4	COOH	CH_2	J65	2	N
904	H	H	A11	COOH	CH_2	J37	2	CH
905	H	H	A11	COOH	CH_2	J63	2	CH
906	H	H	A11	COOH	CH_2	J64	2	CH
907	H	H	A11	COOH	CH_2	J65	2	CH
908	Me	Me	A11	COOH	CH_2	J37	2	CH
909	Me	Me	A11	COOH	CH_2	J63	2	CH
910	Me	Me	A11	COOH	CH_2	J64	2	CH
911	Me	Me	A11	COOH	CH_2	J65	2	CH
912	Cl	Cl	A11	COOH	CH_2	J37	2	CH
913	Cl	Cl	A11	COOH	CH_2	J63	2	CH
914	Cl	Cl	A11	COOH	CH_2	J64	2	CH
915	Cl	Cl	A11	COOH	CH_2	J65	2	CH
916	H	H	A11	COOH	CH_2	J37	2	N
917	H	H	A11	COOH	CH_2	J63	2	N
918	H	H	A11	COOH	CH_2	J64	2	N
919	H	H	A11	COOH	CH_2	J65	2	N
920	Me	Me	A18	COOH	CH_2	J37	2	CH
921	Me	Me	A18	COOH	CH_2	J63	2	CH
922	Me	Me	A18	COOH	CH_2	J64	2	CH
923	Me	Me	A18	COOH	CH_2	J65	2	CH
924	H	H	A18	COOH	CH_2	J37	2	CH
925	H	H	A18	COOH	CH_2	J63	2	CH

Table 38

Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
926	H	H	A18	COOH	CH_2	J64	2	CH
927	H	H	A18	COOH	CH_2	J65	2	CH
928	Cl	Cl	A18	COOH	CH_2	J37	2	CH
929	Cl	Cl	A18	COOH	CH_2	J63	2	CH
930	Cl	Cl	A18	COOH	CH_2	J64	2	CH
931	Cl	Cl	A18	COOH	CH_2	J65	2	CH
932	H	H	A18	COOH	CH_2	J37	2	N
933	H	H	A18	COOH	CH_2	J63	2	N
934	H	H	A18	COOH	CH_2	J64	2	N
935	H	H	A18	COOH	CH_2	J65	2	N
936	Me	Me	A20	COOH	CH_2	J37	2	CH
937	Me	Me	A20	COOH	CH_2	J63	2	CH
938	Me	Me	A20	COOH	CH_2	J64	2	CH
939	Me	Me	A20	COOH	CH_2	J65	2	CH
940	H	H	A20	COOH	CH_2	J37	2	CH
941	H	H	A20	COOH	CH_2	J63	2	CH
942	H	H	A20	COOH	CH_2	J64	2	CH
943	H	H	A20	COOH	CH_2	J65	2	CH
944	Cl	Cl	A20	COOH	CH_2	J37	2	CH
945	Cl	Cl	A20	COOH	CH_2	J63	2	CH
946	Cl	Cl	A20	COOH	CH_2	J64	2	CH
947	Cl	Cl	A20	COOH	CH_2	J65	2	CH
948	H	H	A20	COOH	CH_2	J37	2	N
949	H	H	A20	COOH	CH_2	J63	2	N
950	H	H	A20	COOH	CH_2	J64	2	N

Table 39

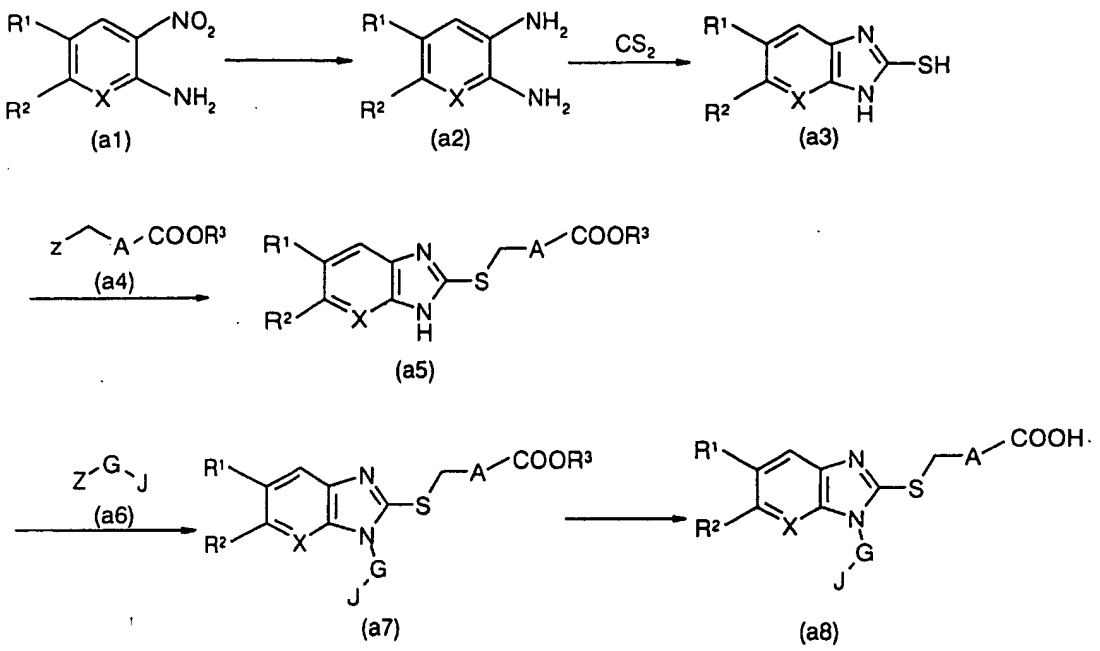
Compound No.	R^1	R^2	SCH_2-A	E	G	J	m	X
951	H	H	A20	COOH	CH_2	J65	2	N
952	Me	Me	A1	tetrazol	CH_2	J37	0	CH
953	Me	Me	A1	tetrazol	CH_2	J63	0	CH
954	Me	Me	A1	tetrazol	CH_2	J64	0	CH
955	Me	Me	A1	tetrazol	CH_2	J65	0	CH
956	H	H	A1	tetrazol	CH_2	J37	0	CH
957	H	H	A1	tetrazol	CH_2	J63	0	CH
958	H	H	A1	tetrazol	CH_2	J64	0	CH
959	H	H	A1	tetrazol	CH_2	J65	0	CH
960	Cl	Cl	A1	tetrazol	CH_2	J37	0	CH
961	Cl	Cl	A1	tetrazol	CH_2	J63	0	CH
962	Cl	Cl	A1	tetrazol	CH_2	J64	0	CH
963	Cl	Cl	A1	tetrazol	CH_2	J65	0	CH
964	H	H	A1	tetrazol	CH_2	J37	0	N
965	H	H	A1	tetrazol	CH_2	J63	0	N
966	H	H	A1	tetrazol	CH_2	J64	0	N
967	H	H	A1	tetrazol	CH_2	J65	0	N
968	H	H	A4	tetrazol	CH_2	J37	0	CH
969	H	H	A4	tetrazol	CH_2	J63	0	CH
970	H	H	A4	tetrazol	CH_2	J64	0	CH
971	H	H	A4	tetrazol	CH_2	J65	0	CH
972	H	H	A18	tetrazol	CH_2	J37	0	CH
973	H	H	A18	tetrazol	CH_2	J63	0	CH
974	H	H	A18	tetrazol	CH_2	J64	0	CH
975	H	H	A18	tetrazol	CH_2	J65	0	CH

Table 40

Compound No.	R'	R'	SCH_2-A	E	G	J	m	X
976	Me	Me	A19	tetrazol	CH_2	J37	0	CH
977	Me	Me	A19	tetrazol	CH_2	J63	0	CH
978	Me	Me	A19	tetrazol	CH_2	J64	0	CH
979	Me	Me	A19	tetrazol	CH_2	J65	0	CH
980	H	H	A19	tetrazol	CH_2	J37	0	CH
981	H	H	A19	tetrazol	CH_2	J63	0	CH
982	H	H	A19	tetrazol	CH_2	J64	0	CH
983	H	H	A19	tetrazol	CH_2	J65	0	CH
984	Me	Me	A20	tetrazol	CH_2	J37	0	CH
985	Me	Me	A20	tetrazol	CH_2	J63	0	CH
986	Me	Me	A20	tetrazol	CH_2	J64	0	CH
987	Me	Me	A20	tetrazol	CH_2	J65	0	CH
988	H	H	A20	tetrazol	CH_2	J37	0	CH
989	H	H	A20	tetrazol	CH_2	J63	0	CH
990	H	H	A20	tetrazol	CH_2	J64	0	CH
991	H	H	A20	tetrazol	CH_2	J65	0	CH

The thiobenzimidazole derivative (1) of the present invention in which E is COOH and m is 0 can be prepared by the synthetic method (A) or (B) shown below:

Synthetic method (A)



wherein Z represents a halogen, R^1, R^2, R^3, A, G, J, and X are as defined above.

Thus, the nitro group of a 2-nitroaniline derivative (a1) is reduced to give an orthophenylene diamine (a2). CS_2 is reacted with this diamine to produce a compound (a3), with which a halide ester derivative (a4) is reacted to obtain (a5). A halide derivative (a6) is reacted therewith to obtain (a7), which is hydrolyzed to yield a benzimidazole derivative (a8) of the present invention.

The reduction of the nitro group may be carried out under a standard condition for catalytic reduction. For example, a reaction is carried out with hydrogen gas in the presence of a catalyst such as Pd-C at a temperature of room temperature to 100°C. Alternatively, a method of treatment using zinc or tin under an acidic condition, or a method of using zinc powder at a neutral or alkaline condition can be used.

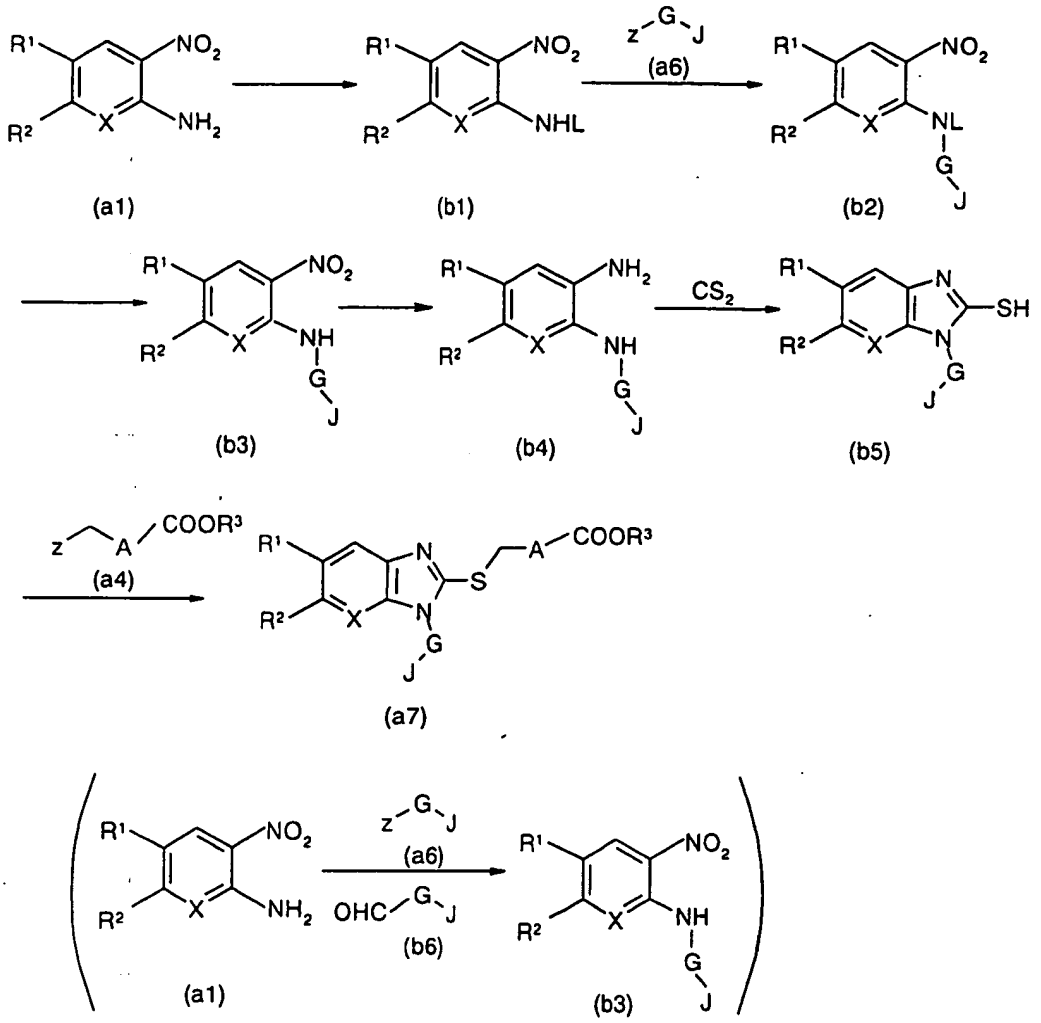
The reaction of an orthophenylene diamine derivative (a2) with CS_2 may be carried out using, for example, a method as described in J. Org. Chem. 19: 631-637, 1954, or J. Med. Chem. 36: 1175-1187, 1993 (EtOH solution).

The reaction of a thiobenzimidazole (a3) and a halide ester (a4) may be carried out according to the condition of the conventional S-alkylation, for example in the presence of a base such as NaH, Et_3N, NaOH, or K_2CO_3 at a temperature of 0°C to 200°C under stirring.

The reaction of a thiobenzimidazole (a5) and a halide derivative (a6) may be carried out according to the condition for the conventional N-alkylation or N-acylation, for example in the presence of a base such as NaH, Et_3N, NaOH, or K_2CO_3 at a temperature of 0°C to 200°C under stirring.

As the elimination reaction of the carboxy protecting group R^3, preferably a method of hydrolysis is employed using an alkali such as lithium hydroxide or an acid such as trifluoroacetic acid.

Synthetic method (B)

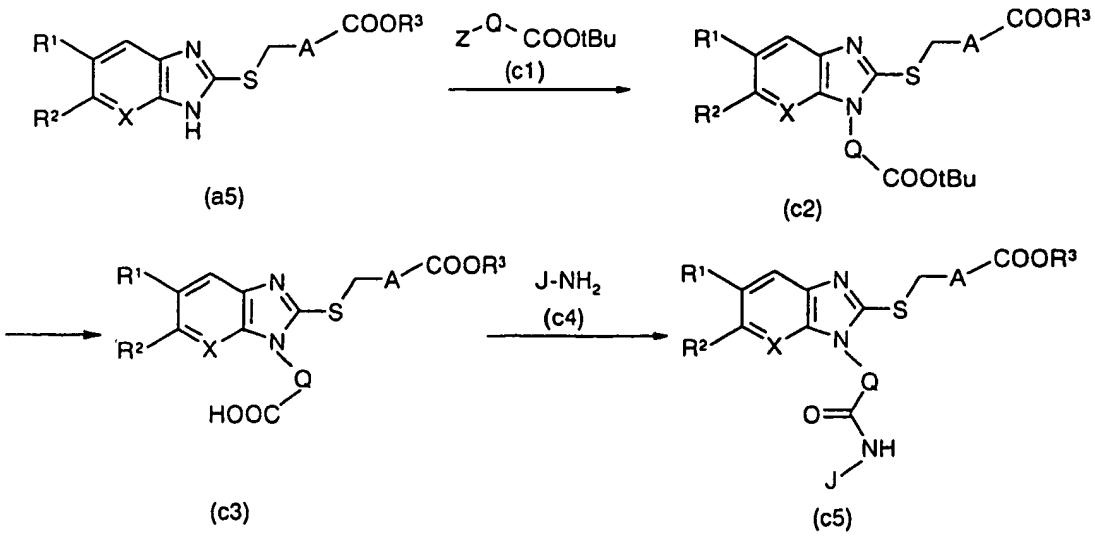


Thus, the amino group of a 2-nitroaniline derivative (a1) can be protected with L to give (b1). A halide derivative (a6) is reacted therewith to obtain (b2), from which L is deprotected to obtain (b3). The nitro group of (b3) is reduced to obtain an orthophenylene diamine derivative (b4). CS_2 is reacted therewith to yield a compound (b5), with which a halide ester derivative (a4) is reacted to obtain (a7) which may be hydrolyzed to yield a benzimidazole derivative of the present invention. Alternatively, it is also possible to obtain a compound (b3) directly by allowing the 2-nitroaniline derivative (a1) as it is unprotected to be reacted to a halide derivative (a6) or an aldehyde derivative (b6).

As the protecting group L, there can be mentioned a trifluoroacetic acetyl group, an acetyl group, a t-butoxycarbonyl group, a benzyl group, and the like. The reaction of the 2-nitroaniline derivative (a1) and the aldehyde derivative (b6) may be carried out according to the conditions of the conventional reductive amination using a reducing agent such as a complex hydrogen compound, for example $LiAlH_4$, $NaBH_4$, NaB_3CN, $NaBH(OAc)_3$, etc. or diborane, in a solvent such as ethanol, methanol, and dichloromethane at a temperature condition of 0°C to 200°C. The other reactions may be carried out as in the Synthetic method (A).

The thiobenzimidazole derivative (1) of the present invention in which E is COOH, m is 0, and G is an amide bond can be prepared by the synthetic method (C) shown below:

Synthetic method (C)



wherein Q represents a methylene group, a phenylene group, etc., and Z represents a halogen. R^1, R^2, R^3, A, J, and X are as defined above, provided that R^3 is a protecting group such as an ethyl group, a methyl group, etc. inactive in an acid.

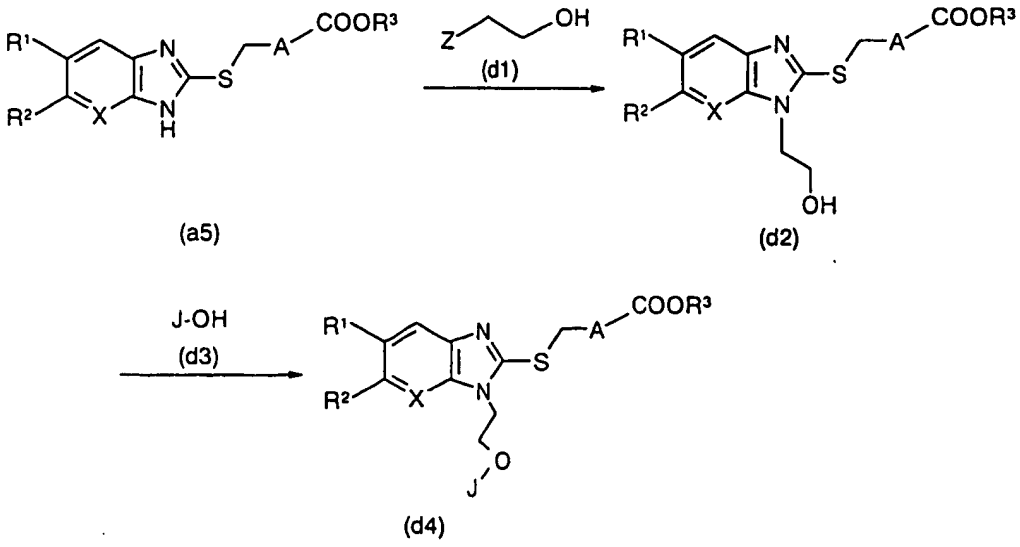
Thus, a tert-butyl ester halide derivative (c1) is reacted with a thiobenzimidazole compound (a5) to obtain

a compound (c2), which is subjected to hydrolysis under an acidic condition to yield (c3). An amine derivative (c4) is reacted therewith to yield (c5), which is subjected to hydrolysis to obtain the benzimidazole derivative of the present invention.

The condensation amidation may be carried out by a conventional method using a condensing agent. As the condensing agent, there can be mentioned DCC, DIPC, EDC=WSCI, WSCI·HCl, BOP, DPPA, etc., which may be used alone or in combination with HONSu, HOBt, HOOBt, etc. The reaction may be carried out in a appropriate solvent such as THF, chloroform, t-butanol, etc. at a temperature condition of 0°C to 200°C. The other reactions may be carried out as in the Synthetic method (A).

The thiobenzimidazole derivative (1) of the present invention in which E is COOH, m is 0, and G is an ether bond can be prepared by the synthetic method (D) shown below:

Synthetic method (D)



wherein Z represents a halogen, R^1, R^2, R^3, A, J, and X are as defined above.

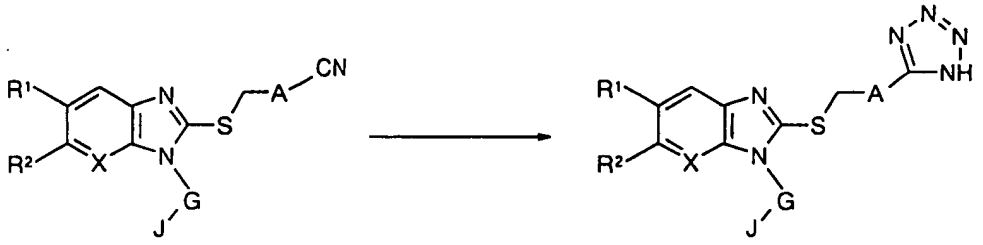
Thus, a thiobenzimidazole compound (a5) is reacted with, for example, a halide alcohol derivative (d1) to yield a compound (d2). A phenol derivative (d3) is

reacted therewith to yield an ether (d4), which is subjected to hydrolysis to yield a benzimidazole derivative (a8) of the present invention.

The etherification may be carried out using a phosphine compound such as triphenyl phosphine and tributyl phosphine and an azo compound such as DEAD and TMAD in a suitable solvent such as N-methylmorpholine and THF at a temperature of 0°C to 200°C in a Mitsunobu reaction or a related reaction thereof. The other reactions may be carried out as in the Synthetic method (A).

The thiobenzimidazole derivative (1) of the present invention in which E is a tetrazole and m is 0 can be prepared by the synthetic method (E) shown below:

Synthetic method (E)



(e1) (e2)

wherein R^1, R^2, A, G, J, and X are as defined above.

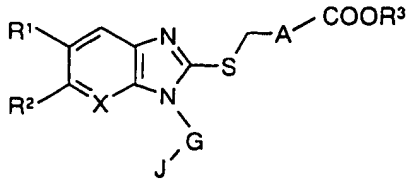
A nitrile (e1) is reacted with various azi compounds to be converted to a tetrazole (e2).

As the azi compound, there can be mentioned a trialkyltin azide compound such as trimethyltin azide, and hydrazoic acid or an ammonium salt thereof. When an organic tin azide compound is used, 1-4 fold molar amount is used relative to the compound (e1). When hydrazoic acid or an ammonium salt thereof is used, 1-5 fold molar amount of sodium azide or a tertiary amine such as ammonium chloride and triethylamine may be used relative to the compound (e1). Each reaction may be carried out at at temperature of 0°C to 200°C in a solvent such as

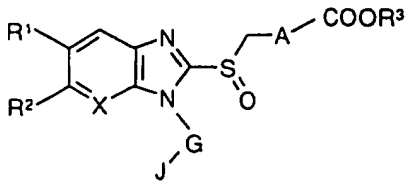
toluene, benzene and DMF.

The thiobenzimidazole derivative (1) of the present invention in which m is 1 or 2 can be prepared by the synthetic method (F) shown below:

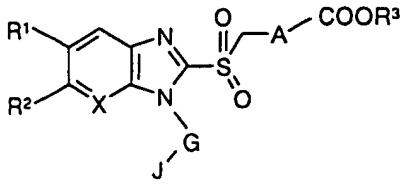
Synthetic method (F)



(a7)



(f1)



(f2)

wherein R^1, R^2, R^3, A, G, J, and X are as defined above.

Thus, a thiobenzimidazole compound (a7) may be reacted with a peroxide compound in a suitable medium to yield a sulfoxide derivative (f1) and/or a sulfone derivative (f2). As the peroxide compound used, there can be mentioned perbenzoic acid, m-chloroperbenzoic acid, peracetic acid, hydrogeny peroxide, and the like, and as the solvent used, there can be mentioned chloroform, dichloromethane, and the like. The ratio of the compound (a7) to the peroxide compound used is selected from, but not limited to, a broad range as appropriate, and generally 1.2 to 5 fold molar amount, for example, may be preferably used. Each reaction is carried out generally at about 0 to 50°C, and preferably at 0°C to room temperature, and is generally complete in about 4-20 hours.

The benzimidazole derivatives of the present invention can be converted, as needed, to medically

acceptable non-toxic cation salts. As such a salt, there can be mentioned an alkali metal ion such as Na^+ and K^+; an alkaline earth metal ion such as Mg^{2+} and Ca^{2+}; a metal ion such as Al^{3+} and Zn^{2+}; or an organic base such as ammonia, triethylamine, ethylenediamine, propanediamine, pyrrolidine, piperidine, piperadine, pyridine, lysine, choline, ethanolamine, N,N-diethylethanolamine, 4-hydroxypiperidine, glucosamine, and N-methylglucamine. Among them, Na^+, Ca^{2+}, lysine, choline, N,N-dimethylethanolamine and N-methylglucamine are preferred.

The benzimidazole derivatives of the present invention inhibit human chymase activity. Specifically, their IC50 is not greater than 1000, preferably not smaller than 0.01 and less than 1000, and more preferably not smaller than 0.05 and less than 500. The benzimidazole derivatives of the present invention having such excellent inhibitory action on human chymase can be used as clinically applicable preventive and/or therapeutic agents for various diseases.

The benzimidazole derivatives of the present invention can be administered as pharmaceutical compositions together with pharmaceutically acceptable carriers by oral or parenteral routes after being shaped into various dosage forms. As the parenteral administration, there can be mentioned intravenous, subcutaneous, intramuscular, percutaneous, rectal, nasal, and eye drop administration.

Dosage forms for said pharmaceutical compositions include the following. For example, in the case of oral administration, there can be mentioned dosage forms such as tablets, pills, granules, powders, solutions, suspensions, syrups, and capsules.

As used herein, tablets are shaped by a conventional method using a pharmaceutically acceptable carrier such as an excipient, a binder, and a disintegrant. Pills, granules, and powders can also be shaped by a conventional method using an excipient etc. Solutions,

suspensions, and syrups may be shaped by a conventional method using glycerin esters, alcohols, water, vegetable oils, and the like. Capsules can be shaped by filling a granule, a powder, and a solution into a capsule made of gelatin etc.

Among the parenteral preparations, those for intravenous, subcutaneous, and intramuscular administration can be administered as an injection. As injections, a benzoic acid derivative is dissolved in a water soluble liquid such as physiological saline, or in a non-water soluble liquid comprising an organic ester such as propylene glycol, polyethylene glycol, and a vegetable oil.

In the case of percutaneous administration, dosage forms such as ointments and creams can be used. Ointments can be prepared by mixing a benzoic acid derivative with a fat or lipid, vaseline, etc., and creams can be prepared by mixing a benzoic acid derivative with an emulsifier.

In the case of rectal administration, gelatin soft capsules can be used to prepare suppositories.

In the case of nasal administration, they can be used as a formulation comprising a liquid or powder composition. As the base for liquid formulations, water, saline, a phosphate buffer, an acetate buffer etc. can be used, and furthermore they may include a surfactant, an antioxidant, a stabilizer, a preservative, and a thickening agent. As the base for powder formulations, there can be mentioned polyacrylic acid salts that are readily solubule in water, cellulose lower alkyl ethers, polyethylene glycol, polyvinylpyrrolidone, amylose, pullulan, etc. that are water-absorptive, or celluloses, starches, proteins, gums, crosslinked vinyl polymers, etc. that are hardly water-soluble, and preferably they are water-absorptive. Alternatively, they may be combined. Furthermore, for powder formulations, an antioxidant, a colorant, a preservative, a disinfectant,

a corrigent, etc. can be added. Such liquid formulations and powder formulations can be administered using, for example, a spraying device etc.

For eye drop administration, they can be used as aqueous or non-aqueous eye drops. For the aqueous eye drops, sterile purified water, physiological saline etc. can be used as a solvent. When sterile purified water is used as the solvent, a suspending agent such as a surfactant and a polymer thickener may be added to prepare an aqueous eye drop suspension. Alternatively, a solubilizing agent such as a nonionic surfactant may be added to prepare a soluble eye drop solution. The non-aqueous eye drop can use a non-aqueous solvent for injection as a solvent, and can be used as a non-aqueous eye drop solution.

In the case where administration to the eye is performed by a method other than the eye drop, dosage forms such as an eye ointment, an application solution, an epipastic, and an insert can be used.

In the case of nasal or oral inhalation, they are inhaled as a solution or a suspension of the benzimidazole derivatives of the present invention with a commonly used pharmaceutical excipient using, for example, an aerosol spray for inhalation, etc. Alternatively, the benzimidazole derivatives of the present invention in a lyophilized powder form can be administered to the lung using an inhaling device that permits direct contact to the lung.

To such various formulations, pharmaceutically acceptable carriers such as an isotonic agent, a preservative, a disinfectant, a wetting agent, a buffering agent, an emulsifier, a dispersant, a stabilizer, etc. can be added as needed.

To these formulations, blending of an antimicrobial agent, a treatment such as filtration through a bacteria-retaining filter, heating, radiation, etc. can be carried out for sterilization. Alternatively, sterile solid

formulations can be prepared, which may be used by dissolving or suspending them in an appropriate sterile solution immediately prior to use.

The dosages of the benzimidazole derivatives of the present invention vary depending on the type of diseases, route of administration, the condition, age, sex, body weight etc. of the patient, but they are generally in the range of about 1 to 500 mg/day/patient for oral administration, and preferably 1 to 300 mg/day/patient. In the case of parenteral administration such as intravenous, subcutaneous, intramuscular, percutaneous, rectal, nasal, eye drop, and inhalation administration, they are about 0.1 to 100 mg/day/patient, and preferably 0.3 to 30 mg/day/patient.

When the benzimidazole derivatives of the present invention are used as a preventive agent, they can be administered according to a known method depending on each condition.

As the target diseases for the preventive and/or therapeutic agents of the present invention, there can be mentioned, for example, diseases of respiratory organs such as bronchial asthma, inflammatory/allergic diseases such as allergic rhinitis, atopic dermatitis, and urticaria; diseases of circulatory organs such as sclerosing vascular lesions, intravascular stenosis, disturbances of peripheral circulation, renal failure, and cardiac failure; diseases of bone/cartilage metabolism such as rheumatoid arthritis and osteoarthritis.

Examples

The present invention will now be explained in more detail with reference to Preparation Examples, Working Examples, and Test Examples. It should be noted, however, that these examples do not limit the scope of the invention in any way.

Reference Example 1. Preparation of 5,6-dimethylbenzimidazole-2-thiol

To 5,6-dimethylorthophenylene diamine (4.5 g, 33 mmol) in pyridine (40 ml) was added carbon disulfide (40 ml, 0.66 mol). The resulting solution was heated to reflux under stirring for 18 hours, to which was added water, followed by extraction with ethyl acetate. After drying the ethyl acetate phase with anhydrous magnesium sulfate, it was concentrated, and dried under reduced pressure at 80°C for 6 hours to obtain the title compound (4.1 g, yield 70%).

Reference Example 2. Preparation of 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl)benzoic acid methyl ester

To the resulting 5,6-dimethylbenzimidazole-2-thiol (89 mg, 0.50 mmol) in dimethylformamide (2 ml), triethylamine (84 µl, 0.6 mmol) and 2-bromomethyl benzoic acid methyl ester (137 mg, 0.6 mmol) were added. After the resulting solution was stirred at 80°C for 1.5 hours, water was added, followed by extraction with ethyl acetate. After drying the ethyl acetate phase with anhydrous magnesium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to obtain the title compound (146 mg, yield 90%). The compound was confirmed by identification of molecular weight using LC-MS. Calculated M = 326.11, measured $(M+H)^+$ = 327.2

Reference Example 3.

In a similar manner to Reference Example 2, the following compounds were synthesized. The compounds were confirmed by identification of molecular weight using LC-MS.

3-((5,6-dimethylbenzimidazole-2-ylthio)methyl)pyridine-2-carboxylic acid ethyl ester

Calculated M = 341.12, found $(M+H)^+$ = 342.2

2-((5,6-dimethylbenzimidazole-2-

ylthio)methyl)furane-3-carboxylic acid methyl ester

Calculated M = 316.09, found $(M+H)^+$ = 317.2

3-((5,6-dimethylbenzimidazole-2-ylthio)methyl)thiphene-2-carboxylic acid methyl ester

Calculated M = 332.07, found $(M+H)^+$ = 333.2

2-(benzimidazole-2-ylthiomethyl)benzoic acid methyl ester

Calculated M = 298.08, found $(M+H)^+$ = 299.2

3-(benzimidazole-2-ylthiomethyl)pyridine-2-carboxylic acid ethyl ester

Calculated M = 313.09, found $(M+H)^+$ = 314.2

3-(benzimidazole-2-ylthiomethyl)thiophene-2-carboxylic acid methyl ester

Calculated M = 304.03, found $(M+H)^+$ = 305.2

2-(benzimidazole-2-ylthiomethyl)furane-3-carboxylic acid methyl ester

Calculated M = 288.06, found $(M+H)^+$ = 289.2

4-benzimidazole-2-ylthiobutanoic acid methyl ester

Calculated M = 264.09, found $(M+H)^+$ = 265.2

2-((5,6-dichlorobenzimidazole-2-ylthio)methyl)-5-chlorobenzoic acid methyl ester

Calculated M = 399.96, found $(M+H)^+$ = 401.2

2-(benzimidazole-2-ylthiomethyl)-5-chlorobenzoic acid methyl ester

Calculated M = 332.04, found $(M+H)^+$ = 333.2

4-((5,6-dimethylbenzimidazole-2-ylthio)butanoic acid ethyl ester

Calculated M = 292.12, found $(M+H)^+$ = 293.40

2-((5,6-dichlorobenzimidazole-2-ylthio)methyl)-benzoic acid methyl ester

Calculated M = 366.00, found $(M+H)^+$ = 367.0

2-((5,6-dichlorobenzimidazole-2-ylthio)methyl)pyridine-3-carboxylic acid methyl ester

Calculated M = 366.99, found $(M+H)^+$ = 368.0

Example 1 Preparation of compound No. 143

Sodium hydride (11 mg, 0.306 mmol) and 2 ml of tetrahydrofuran was added to a previously dried reaction

vessel. To the mixture were added 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl)benzoic acid methyl ester (50 mg, 0.153 mmol) and 1-chloromethylnaphthalene (69 µl, 0.459 mmol), which was then stirred at 60°C for 45 minutes. Water was added thereto, followed by extraction with ethyl acetate. After drying the ethyl acetate phase with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 2-((5,6-dimethyl-1-(1-naphthylmethyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (yield 32%).

To 2-((5,6-dimethyl-1-(1-naphthylmethyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (23 mg, 0.08 mmol) in tetrahydrofuran (1 ml) and methanol (0.5 ml), 4N aqueous sodium hydroxide solution (o.25 ml) was added. After stirring at room temperature for 5 hours, 6N hydrochloric acid was added to stop the reaction, followed by extraction with ethyl acetate. The ethyl acetate phase was washed with saturated saline, and then dried in anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain the title compound (24 mg, yield quantitative).

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 452.16, found $(M+H)^+$ = 453.2

Example 2.

In a similar manner to Working Example 1, the compounds in Tables 41 to 45 were synthesized using the compounds in Reference Examples 2 or 3 and various halide derivatives. The compounds were confirmed by identification of molecular weight using LC-MS.

Table 41

Compound No.	Calculated M	Found $(M+H)^+$	Recovery % (overall)
390	406.14	407.2	29
391	422.11	423.2	16
315	417.15	418.2	32
376	406.14	407.2	25
333	417.15	418.2	6
82	416.16	417.2	12
83	416.16	417.2	9
84	416.16	417.2	33
97	432.15	433.2	18
98	432.15	433.2	26
99	432.15	433.2	8
94	470.13	471.2	14
95	470.13	471.2	10
96	470.13	471.2	13
100	486.12	487.2	26
101	486.12	487.2	8
85	420.13	421.2	9
86	420.13	421.0	12
87	420.13	421.2	44
88	436.10	437.2	42
89	436.10	437.2	40
90	436.10	437.2	28
91	480.07	481.0	12
103	427.14	428.2	12
104	427.14	428.2	6
105	427.14	428.2	11
784	434.11	435.2	36

Table 42

Compound No.	Calculated M	Found $(M+H)^+$	Recovery (overall) %
787	468.07	469.2	31
112	418.14	419.2	40
141	480.12	481.0	72
138	494.17	495.2	34
135	446.13	447.2	19
137	478.17	479.2	6
143	452.16	453.2	35
142	452.16	453.0	30
139	428.16	429.4	22
140	458.20	459.2	5
63	424.12	425.2	25
311	453.15	454.5	21
115	430.17	431.5	68
116	430.17	431.5	52
117	430.17	431.5	41
118	430.17	431.5	56
125	462.16	463.0	59
126	462.16	463.0	25
128	492.17	493.0	27
134	446.13	447.0	34
108	446.17	447.0	75
107	446.17	447.0	57
119	470.06	471.0	36
120	470.06	471.0	57
121	470.06	471.0	60
122	470.06	471.0	37
123	430.17	431.3	57

Table 43

Compound No.	Calculated M	Found $(M+H)^+$	Recovery (overall) %
124	462.16	463.3	67
127	462.16	463.3	62
129	446.17	447.3	47
130	446.17	447.3	40
319	425.12	426.3	30
506	466.17	467.2	16
505	466.17	467.0	14
93	480.07	481.0	45
136	478.17	479.2	60
37	402.14	403.4	25
39	442.03	443.0	51
317	403.14	404.0	56
318	443.03	444.0	46
380	442.14	443.2	51
377	420.15	421.2	34
378	460.04	461.0	30
386	414.10	415.2	37
383	392.12	393.2	30
384	432.01	433.0	29
395	458.11	459.2	23
392	436.13	437.2	15
393	476.02	477.0	15
401	430.08	431.2	50
398	408.10	409.2	20
399	447.99	449.0	7

Table 44

Compound No.	Calculated M	Found $(M+H)^+$	Recovery % (overall)
544	476.18	377.2	62
50	418.14	419.2	42
459	382.08	383.2	65
402	436.04	437.2	50
1	388.12	389.0	38
161	456.05	457.0	54
81	402.14	403.3	57
154	444.13	445.0	32
160	408.10	409.0	72
159	421.15	422.2	84
148	482.17	483.5	64
149	453.15	454.5	71
155	459.11	460.0	64
150	453.15	454.2	36
151	487.11	488.1	62
153	460.10	461.0	69
152	454.15	455.0	62
64	430.08	431.2	85
455	410.11	411.2	17
596	430.14	431.2	56
539	418.17	419.2	20
349	436.10	437.1	50
352	458.09	459.2	74
168	470.06	471.1	57
355	504.02	505.0	26
174	492.05	493.0	89
358	526.01	527.1	38

Table 45

Compound No.	Calculated M	Found $(M+H)^+$	Recovery (overall) %
324	493.04	494.2	32
320	431.08	432.1	15
147	466.17	467.2	72
616	490.16	491.2	22
805	382.17	383.2	52
804	368.16	369.2	56
66	438.14	440.2	54
592	430.14	432.3	5
811	380.16	382.2	72
582	436.06	437.1	59
580	436.06	437.1	59
584	480.03	483.1	37
583	480.03	483.0	52
578	420.09	421.2	30
574	416.12	417.2	39
595	452.12	453.2	22
594	478.14	479.1	23
588	432.11	433.1	65
587	432.11	433.2	48
586	432.11	433.1	50
590	427.10	428.2	24
589	427.10	428.3	17

Example 3. Preparation of compound No. 547

Triethylamine (276 µl, 1.98 mmol) and 2-(bromoethyl)benzoic acid t-butyl ester (538 mg, 1.99 mmol) were added to 5,6-dimethylbenzimidazole-2-thiol (236 mg, 1.32 mmol) in 2 ml of dimethylformamide, which was then stirred at 80°C for 3 hours. After the reaction was complete, water was added, followed by extraction with ethyl acetate. After drying the ethyl acetate phase with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to obtain 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl)benzoic acid t-butyl ester (288 mg, yield 59%).

2-((5,6-dimethylbenzimidazole-2-ylthio)methyl)benzoic acid t-butyl ester (30 mg, 0.082 mmol) was dissolved in 3 ml of chloroform, to which triethylamine (17 µl, 0.123 mmol) and benzoyl chloride (14 µl, 0.123 mmol) were sequentially added and the mixture was stirred at room temperature for 2 hours. After the reaction was complete, water was added, followed by extraction with ethyl acetate. After drying the ethyl acetate phase with anhydrous sodium sulfate, it was concentrated, and 2-((5,6-dimethyl-1-(phenylcarbonyl)benzimidazole-2-ylthio)methyl)benzoic acid t-butyl ester was obtained (38 mg, yield quantitative).

2-((5,6-dimethyl-1-(phenylcarbonyl)benzimidazole-2-ylthio)methyl)benzoic acid t-butyl ester was dissolved in 1 ml of dichloromethane, to which trifluoroacetic acid (1 ml) was added and the mixture was stirred at room temperature for 6 hours. After the reaction was complete, the solvent was evaporated under reduced pressure and dried overnight to obtain the title compound (33 mg, yield quantitative).

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 416.12, found $(M+H)^+$ = 417.0

Example 4. Preparation of compound No. 561

The title compound was obtained in a similar manner to Working Example 3.

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 452.09, found $(M+H)^+$ = 453.2

Reference Example 4. Preparation of 3-(naphthylmethyl)imidazolo(5,4-b)pyridine-2-thiol

To 2-amino-3-nitropyridine (1680 mg, 12 mmol) in a dimethylformamide (20 ml), sodium hydride (75 mg, 0.55 mmol) and 1-chloromethylnaphthalene (74 µl, 0.55 mmol) were added. After the resulting solution was stirred at 80°C for 17 hours, water was added thereto, followed by extraction with ethyl ether. After drying the ethyl ether phase with anhydrous magnesium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain of naphthylmethyl(3-nitro(2-pyridil))amine (903 mg, yield 27%).

To naphthylmethyl(3-nitro(2-pyridil))amine (900 mg, 3.2 mmol) in ethanol (40 ml), 90.0 mg of 10% Pd-C was added. After the resulting solution was stirred in a hydrogen atmosphere at 50°C for 8 hours, it was filtered through celite to remove Pd-C. The resulting solution was concentrated to obtain (3-amino(2-pyridil))naphthylmethylamine (860 mg, yield 99%). To the resulting (3-amino(2-pyridil))naphthylmethylamine (860 mg, 3.2 mmol) in ethanol (20 ml), carbon disulfide (6.1 ml, 102 mmol) was added. After the resulting solution was heated to reflux under stirring for 12 hours, it was allowed to stand at room temperature for 5 hours. The precipitate that deposited was filtered, and was washed three times with ethanol (5 ml). It was dried at 80°C under reduced pressure for 5 hours to obtain the title compound (555 mg, yield 56%)

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 291.08, found $(M+H)^+$ = 292.3

Reference Example 5. Preparation of 3-((2,5-dimethylphenyl)methyl)imidazolo(5,4-b)pyridine-2-thiol

The title compound was synthesized in a similar manner to Reference Example 4.

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 269.01, found $(M+H)^+$ = 270.2

Example 5. Preparation of compound No. 256

Using 3-(naphthylmethyl)imidazolo(5,4-b)pyridine-2-thiol (30 mg, 0.1 mmol) obtained in Reference Example 4 in a similar manner to Reference Example 2, 2-((3-(naphthylmethyl)imidazolo(5,4-b)pyridine-2-ylthio)methyl)benzoic acid methyl ester was obtained (30 mg, yield 70%).

The 2-((3-(naphthylmethyl)imidazolo(5,4-b)pyridine-2-thio)methyl)benzoic acid methyl ester (30 mg, 0.068 mmol) thus obtained was subjected to hydrolysis in a similar manner to Example 1 to obtain the title compound (18.3 mg, yield 66%).

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 425.12, found $(M+H)^+$ = 426.1

Example 6.

The compounds in Table 46 were synthesized using the compounds obtained in Reference Examples 4 and 5 and various halide ester derivatives in a similar manner to Example 5.

The compounds were confirmed by identification of molecular weight using LC-MS.

Table 46

Compound No.	Calculated M	Found $(M+H)^+$	Yield (Overall) %
253	403.14	407.2	67
327	404.13	423.2	46
329	426.12	418.2	58
361	437.10	438.0	52
364	459.08	460.0	66

Table 47

Compound No.	Calculated M	Found $(M+H)^+$	Yield (Overall) %
321	428.13	429.2	27
354	461.10	462.2	20
460	379.14	380.2	19

Table 48

Compound No.	Calculated M	Found $(M+H)^+$	Yield (Overall) %
52	493.15	494.2	12
53	493.15	494.2	11

Example 7. Preparation of compound No. 264

4-methyl-2-nitroaniline (913 mg, 6 mmol) was dissolved in acetonitrile (18 ml), to which anhydrous trifluoroacetic acid (1.00 ml, 7.2 mmol) was added and the mixture was subjected to reflux for 1.5 hours. After cooling to room temperature, it was concentrated under reduced pressure and dried to obtain 4-methyl-2-nitro trifluoroacetanilide (1.396 g, yield 94%).

4-methyl-2-nitro trifluoroacetanilide (1.396 g, 5.63 mmol) was dissolved in dimethylformamide (14 ml), and then potassium carbonate (940 mg, 6.80 mmol) and 1-chloromethylnaphthalene (1.15 g, 6.51 mmol) were sequentially added at room temperature and heated to 100°C. After 1 hour and 40 minutes, 5N aqueous sodium hydroxide solution (7.5 ml) was added and refluxed as it was for 15 minutes. After 15 minutes, it was cooled to room temperature, and water (180 ml) was added and stored at 4°C overnight. The crystals that deposited were filtered and were dried to obtain ((1-naphthyl)methyl)(4-

methyl-2-nitro-phenyl)amine (1.587 g, yield 96%).

To (1-naphthyl)methyl)(4-methyl-2-nitro-phenyl)amine (1.0021 g, 3.43 mmol), ethanol (5 ml) and 1,4-dioxane (5 ml) were added, and 2.058 M aqueous sodium hydroxide solution (1 ml) was further added, and refluxed in an oil bath. After 15 minutes, it was removed from the oil bath, and zinc powder (897 mg, 13.72 mmol) was fed thereto in portions. Then it was refluxed again in the oil bath for 2 hours. After 2 hours, it was concentrated under reduced pressure, and dissolved in ethyl acetate (50 ml), and washed twice with saturated saline (25 ml). After drying with magnesium sulfate, it was concentrated under reduced pressure and dried to obtain a brown oil of ((1-naphthyl)methyl)(2-amino-4-methyl-phenyl)amine (943.1 mg).

Subsequently, ((1-naphthyl)methyl)(2-amino-4-methyl-phenyl)amine (943.1 mg, 3.59 mmol) was dissolved in ethanol (6.4 ml), to which carbon bisulfide (7 ml, 116 mmol) was added, and then refluxed. After 10 hours, it was returned to room temperature, concentrated under reduced pressure. Ethanol (2 ml) was added to the residue, which was stirred at room temperature for 30 minutes, and was further stirred on ice for 30 minutes. The resulting crystals were filtered, and dried to obtain 1-((1-naphthyl)methyl)-6-methyl-benzimidazole-2-thiol (459.1 mg, yield 44%, 2 steps).

1-((1-naphthyl)methyl)-6-methyl-benzimidazole-2-thiol (431.1 mg, 1.42 mmol) was dissolved in dimethylformamide (12 ml), to which triethylamine (0.296 ml, 2.12 mmol) and 2-bromomethyl benzoic acid methyl ester (390.1 mg, 1.70 mmol) were added and heated to 80°C. After 5 hours and 50 minutes, triethylamine (0.296 ml, 2.12 mmol) and 2-bromomethyl benzoic acid methyl ester (325 mg, 1.42 mmol) were added, and heated for 1 hour and 10 minutes. Thereafter, it was concentrated under reduced pressure, and dissolved in ethyl acetate (80 ml), washed twice with water (30 ml), and dried in

magnesium sulfate. The solvent was concentrated under reduced pressure. The residue was crystallized in ethyl acetate-hexane to obtain 410 mg, and the mother liquor was purified by silica gel column chromatography (hexane : ethyl acetate = 6:1) to recover 87 mg of the same fraction as the crystals, with a total of 497 mg of 2-((1-((1-naphthyl)methyl)-6-methyl-benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (yield 78%).

2-((1-((1-naphthyl)methyl)-6-methyl-benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (497 mg, 1.098 mmol) was dissolved in methanol (10 ml) and tetrahydrofuran (10 ml), to which 4N aqueous lithium hydroxide solution (6.86 ml) was added. After stirring at room temperature for 2 hours and 30 minutes, saturated aqueous citric acid solution (10 ml) was added thereto to stop the reaction, and the mixture was concentrated under reduced pressure to reduce the amount of the solvent to about 1/3, which was dissolved in ethyl acetate (80 ml) and washed five times with water (20 ml). After concentrating the organic layer under reduced pressure, acetonitrile (10 ml) was added to the residue, which was again concentrated under reduced pressure, and the resulting crystals were filtered off and dried to obtain the title compound (439.1 mg, yield 91%).

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 438.14, found $(M+H)^+$ = 439.3

Example 8. Preparation of compound No. 272

In a similar method to Working Example 7, the title compound was obtained.

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 454.14, found $(M+H)^+$ = 455.3

Example 9. Preparation of compound No. 65

2-nitroaniline (829 mg, 6 mmol) and 1-methylindole carboxaldehyde (1242 mg, 7.8 mmol) were dissolved in 20 ml of tetrahydrofuran, to which acetic acid (200 µl) and

$NaBH(OAc)_3$ (5087 mg, 24 mmol) were sequentially added and stirred at room temperature overnight. A saturated aqueous sodium hydrogen carbonate solution was added thereto, followed by extraction with ethyl acetate, dried with anhydrous sodium sulfate, and the solvent was evaporated. After purification by silica gel column chromatography (hexane : ethyl acetate = 95:5), ((1-methylindole-3-yl)methyl)(2-nitrophenyl)amine was obtained (264 mg, yield 18%).

((1-methylindole-3-yl)methyl)(2-aminophenyl)amine (264 mg, 0.939 mmol) was dissolved in ethanol (10 ml), and Pd-C (50 mg, 10% Pd, 0.047 mmol) was added thereto, and stirred in hydrogen atmosphere at room temperature for 6 hours. After the reaction was complete, Pd-C was filtered off and the solvent was evaporated to obtain ((1-methylindole-3-yl)methyl)(2-aminophenyl)amine (212 mg, yield 90%).

((1-methylindole-3-yl)methyl)(2-aminophenyl)amine (212 mg, 0.845 mmol) was dissolved in pyridine (1 ml), and carbon bisulfide (1 ml, 16.9 mmol) was added thereto. The mixture was refluxed in nitrogen atmosphere for 1 hour. After the solvent was evaporated, it was purified by silica gel column chromatography (hexane : ethyl acetate = 2:1) to obtain ((1-methylindole-3-yl)methyl)benzimidazole-2-thiol (96 mg, yield 39%).

Sodium hydride (12 mg, 0.342 mmol) and dimethylformamide (2 ml) were added to a previously dried reaction vessel. To the mixture were added ((1-methylindole-3-yl)methyl)benzimidazole-2-thiol (50 mg, 0.171 mmol) and 2-bromomethyl benzoic acid methyl ester (59 mg, 0.257 mmol), and then the mixture was stirred at 60°C for 1 hour. Water was added thereto, followed by extraction with ethyl acetate. After the ethyl acetate phase was dried with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2:1) to obtain 2-((1-((-methylindole-3-yl)methyl)benzimidazole-2-

ylthio)methyl)benzoic acid methyl ester (54 mg, yield 74%).

To 2-((1-((1-methylindole-3-yl)methyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (54 mg, 0.122 mmol) in tetrahydrofuran (2 ml) and methanol (1 ml), 4N aqueous lithium hydroxide solution (0.5 ml) was added. After stirring at room temperature overnight, 6N hydrochloric acid was added to stop the reaction, followed by extraction with ethyl acetate. After washing the ethyl acetate phase with saturated saline, it was dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain the title compound (48 mg, yield 92%).

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 427.14, found $(M+H)^+$ = 428.2

Example 10.

The compounds in the above Table 47 were synthesized using various halide ester derivatives in a similar manner to Working Example 9. The compounds were confirmed by identification of molecular weight using LC-MS.

Example 11. Preparation of compound No. 51

Sodium hydride (104 mg, 2.86 mmol) and tetrahydrofuran (16 ml) were added to a previously dried reaction vessel. To the mixture were added 2-(benzimidazole-2-ylthiomethyl)benzoic acid methyl ester (428 mg, 1.43 mmol) and 2-(bromomethyl)benzoic acid t-butyl ester (466 mg, 3.46 mmol), and then the mixture was stirred at 60°C for 50 minutes. Water was added thereto, followed by extraction with ethyl acetate. After the ethyl acetate phase was dried with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3:1) to obtain 2-((1-((2-((t-butyl)oxycarbonyl)phenyl)methyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (495 mg, yield

71%).

To 2-((1-((2-((t-butyl)oxycarbonyl)phenyl)methyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (248 mg, 0.51 mmol), 4N hydrochloric acid in dioxane (1.28 ml, 5.1 mmol) was added, and stirred at room temperature overnight. After the solvent was evaporated, it was dried under reduced pressure to obtain 2-((2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazolyl)methyl) benzoic acid (220 mg, yield quantitative).

2-((2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazolyl)methyl) benzoic acid (180 mg, 0.42 mmol) was dissolved in chloroform (6 ml), to which HOBT (68 mg, 0.504 mmol), aniline (46 µl, 0.504 mmol), t-butanol (1.2 ml) and EDCI (97 mg, 0.504 mmol) were sequentially added and stirred overnight at room temperature. Water was added thereto, followed by extraction with dichloromethane. After drying with anhydrous sodium sulfate, it was filtered, and the solvent was evaporated. It was purified by silica gel column chromatography (hexane : ethyl acetate = 3:2) to obtain 2-((1-((2-(N-phenylcarbamoyl)phenyl)methylthio)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (86 mg, yield 40%).

To the thus obtained 2-((1-((2-(N-phenylcarbamoyl)phenyl)methylthio)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (86 mg, 0.169 mmol) in tetrahydrofuran (2 ml) and methanol (1 ml), 4N aqueous lithium hydroxide solution (0.5 ml) was added, and stirred at 60°C for about 2 hours. 6N aqueous hydrochloric acid solution was added to stop the reaction, which was extracted with ethyl acetate. After washing the ethyl acetate phase with saturated saline, it was dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain the title compound (83 mg, yield quantitative).

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 493.15, found $(M+H)^+$ = 494.2

Example 12.

In a similar method to Working Example 11, the compounds shown in the above Table 48 were obtained using various benzoic acid ester derivatives.

The compounds were confirmed by identification of molecular weight using LC-MS.

Example 13. Preparation of compound No. 619

Sodium hydride (400 mg, 10.0 mmol) and dimethylformamide (30 ml) were added to a previously dried reaction vessel. To the mixture were added 2-(benzimidazole-2-ylthiomethyl)benzoic acid methyl ester (1500 mg, 5.0 mmol) and bromoacetate t-butyl ester (1463 mg, 7.5 mmol), and the mixture was stirred at 80°C for 2 hours. Water was added thereto, followed by extraction with ether. After the ether phase was dried with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 5:1) to obtain 2-(2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazolyl)acetic acid t-butyl ester (1298 mg, yield 63%).

To 2-(2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazolyl)acetic acid t-butyl ester (1290 mg, 3.13 mmol), trifluoroacetic acid (15 ml) was added, and stirred at room temperature overnight. After the solvent was evaporated, it was dried under reduced pressure to obtain 2-(2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazolyl)acetic acid (715 mg, yield 64%).

2-(2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazolyl)acetic acid (35 mg, 0.1 mmol) was dissolved in tetrahydrofuran (3 ml), to which aniline (11.2 mg, 0.12 mmol) and EDCI (23 mg, 0.12 mmol) were added, and then the mixture was stirred overnight at room temperature. Water was added

thereto, followed by extraction with ethyl acetate. After drying with anhydrous sodium sulfate, it was filtered, the solvent was evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3:2) to obtain 2-((1-((N-phenylcarbamoyl)methyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (27.5 mg, yield 64%).

2-((1-((N-phenylcarbamoyl)methyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (20 mg, 0.046 mmol) thus obtained was subjected to hydrolysis as in Working Example 1 to obtain the title compound (6.9 mg, yield 36%).

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 417.11, found $(M+H)^+$ = 418.0

Example 14

In a similar method to Example 13, the compounds shown in the above Table 49 were obtained using various aniline derivatives.

The compounds were confirmed by identification of molecular weight using LC-MS.

Table 49

Compound No.	Calculated M	Found $(M+H)^+$	Yield (Overall) %
622	431.13	432.3	5
621	431.13	432.3	5
620	431.13	432.3	21
637	447.13	448.2	13
636	117.13	448.1	23
635	447.13	448.3	44
642	442.11	443.2	27
657	467.13	488.1	19

Table 50

Compound No.	Calculated M	Found $(M+H)^+$	Yield (Overall) %
765	457.15	458.2	5
767	457.15	458.2	32

Table 51

Compound No.	Calculated M	Found $(M+H)^+$	Yield (Overall) %
866	434.13	435.2	76
869	456.11	457.3	83
904	468.09	469.1	52
937	436.15	437.2	61

Table 52

Compound No.	Calculated M	Found $(M+H)^+$	Yield (Overall) %
953	476.18	477.2	36
985	428.18	429.2	67
977	400.15	401.4	2

Reference Example 6. Preparation of 2-((1-(2-hydroxyethyl)-5,6-dimethylbenzimidazole-2-ylthio)]methyl)benzoic acid methyl ester

To 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl) benzoic acid methyl ester (326 mg, 1 mmol) obtained in Reference Example 2 in dimethylformamide, potassium carbonate (207 mg, 1.5 mmol) and 2-bromoethanol (150 mg, 1.2 mmol) were added, and the resulting solution was stirred at 80°C for 12 hours. After the reaction was complete, it was extracted with ether and the solvent was evaporated. The residue was purified by a flash column chromatography (hexane : ethyl acetate = 4:1) to obtain the the title compound (248 mg, yield 67%).

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 370.14, found $(M+H)^+$ = 371.2

Example 15. Preparation of compound No. 736

To 2-((1-(2-hydroxyethyl)-5,6-dimethylbenzimidazole-2-ylthio)methyl)benzoic acid methyl ester (45 mg, 0.23 mmol) in N-methylmorpholine (3 ml), Pph_3 (62 mg, 0.24 mmol) and DEAD (10.6 ml, 40% in toluene, 0.24 mmol) were added and the mixture was stirred at room temperature.

After 10 minutes, phenol (11.3 mg, 0.12 mmol) was added thereto, which was stirred at room temperature for 12 hours. The solvent was evaporated and the residue was purified by thin layer chromatography (hexane : ethyl acetate = 1:1) to obtain 2-((5,6-dimethyl-1-(2-phenoxyethyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (44 mg, yield 81%).

Using 2-((5,6-dimethyl-1-(2-phenoxyethyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (35 mg, 0.078 mmol) in a similar method to Example 1, a hydrolysis reaction was carried out to obtain the title compound (31 mg, yield 94%). The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 432.15, found $(M+H)^+$ = 433.2

Example 16.

In a similar method to Example 15, the compounds shown in the above Table 50 were obtained using various phenol derivatives.

The compounds were confirmed by identification of molecular weight using LC-MS.

Example 17.

Preparation of compound No. 825

To an ester (33 mg, 0.075 mmol) of compound No. 68 obtained in Example 2 in dichloromethane, 50 to 60% m-chloroperbenzoic acid (26 mg, 0.083 mmol) was added while cooling on ice. After the resulting solution was stirred on ice for 2 hours, a saturated sodium hydrogen carbonate solution was poured and the solution obtained was extracted with chloroform. After washing the chloroform phase with water, it was concentrated and the residue was purified by thin layer chromatography (hexane : ethyl acetate = 1:1) to obtain 2-(((5,6-dimethyl-1-(1-naphthylmethyl)benzimidazole-2-yl)sulfinyl)methyl)benzoic acid methyl ester (7.1 mg, yield 21%).

In a manner similar to Example 1, this was subjected to hydrolysis to obtain the title compound (5.2 mg, yield

76%).

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 440.12, found $(M+H)^+$ = 441.3

Example 18. Preparation of compound No. 869

To an ester (39 mg, 0.094 mmol) of compound No. 37 obtained in Example 2 in dichloromethane (5 ml), 50 to 60% m-chloroperbenzoic acid (64 mg, 0.374 mmol) was added while cooling on ice. After the resulting solution was stirred at room temperature for 4 hours, a saturated sodium hydrogen carbonate solution was poured and the solution obtained was extracted with chloroform. After washing the chloroform phase with water, it was concentrated and the residue was purified by flash layer chromatography (hexane : ethyl acetate = 5:1) to obtain 2-(((1-((2,5-dimethylphenyl)methyl)benzimidazole-2-yl)sulfonyl)methyl)benzoic acid methyl ester (37 mg, yield 87%).

In a manner similar to Example 1, 2-(((1-((2,5-dimethylphenyl)methyl)benzimidazole-2-yl)sulfonyl)methyl)benzoic acid methyl ester (64 mg, 0.14 mmol) was subjected to hydrolysis to obtain the title compound (53 mg, yield 87%).

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 434.13, measured $(M+H)^+$ = 435.2

Example 19.

In a manner similar to Example 18, the compounds shown in the above Table 51 were synthesized using the esters of the compounds obtained in Working Example 2. The compounds were confirmed by identification of molecular weight using LC-MS.

Example 20. Preparation of compound No. 952

To 5,6-dimethylbenzimidazole-2-thiol (713 mg, 4 mmol) in dimethylformamide (10 ml), triethylamine (836 µl, 6 mmol) and 2-bromomethylbenzonitrile (1176 mg, 6 mmol) were added. After stirring at 80°C overnight,

water was added to the mixture, followed by extraction with ethyl acetate. After the ethyl acetate phase was dried with anhydrous sodium sulfate, it was concentrated and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3:2) to obtain 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl)benzenecarbonitrile (1159 mg, yield 99%).

Sodium hydride (178 mg, 4.90 mmol) and tetrahydrofuran (30 ml) were added to a previously dried reaction vessel. To the mixture were added 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl)benzenecarbonitrile (719 mg, 2.45 mmol) and 2,5-dichlorobenzyl chloride (543 µl, 4.90 mmol), and the mixture was stirred at 60°C for 40 minutes. Water was added thereto, followed by extraction with ethyl acetate. After the ethyl acetate phase was dried with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3:1) to obtain 2-((1-((2,5-dimethylphenyl)methyl)-5,6-dimethylbenzimidazole-2-ylthio)methyl)benzenecarbonitrile (370 mg, yield 37%).

2-((1-((2,5-dimethylphenyl)methyl)-5,6-dimethylbenzimidazole-2-ylthio)methyl)benzenecarbonitrile (165 mg, 0.401 mmol) was dissolved in toluene (3 ml), to which Me_3SnN_3 (124 mg, 0.602 mmol) was added, and refluxed in nitrogen atmosphere overnight. After the reaction was complete, the solvent was evaporated, and the residue was purifed by silica gel column chromatography (dichloromethane : methanol = 19:1) to obtain the title compound (75 mg, yield 41%).

The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 454.19, found $(M+H)^+$ = 455.2

Example 21.

In a manner similar to Example 20, the compounds shown in the above Table 52 were obtained.

The compounds were confirmed by identification of

molecular weight using LC-MS.

Example 22. Preparation of recombinant human mast cell chymase

Recombinant pro-type human mast cell chymase was prepared according to the method reported by Urada et al. (Journal of Biological Chemistry 266: 17173, 1991). Thus, a culture supernatant of the insect cell (Tn5) infected with a recombinant baculovirus containing cDNA encoding human mast cell chymase was purified by heparin Sepharose (Pharmacia). After it was further activated by the method reported by Murakami et al. (Journal of Biological Chemistry 270: 2218, 1995), it was purified with heparin Sepharose to obtain an activated human mast cell chymase.

Example 23. Determination of the activity of inhibiting recombinant human mast cell chymase

After a DMSO solution (2 µl) containing the compound of the present invention was added to 50 µl of buffer A (0.5-3.0 M NaCl, 50 mM Tris-HCl, pH 8.0) containing 1-5 ng of the activated human mast cell chymase obtained in Working Example 22, 50 µl of buffer A containing, as a substrate, 0.5 mM succinyl-alanyl-histidyl-prolyl-phenylalanylparanitroanilide (Bacchem) was added thereto and the mixture was allowed to react at room temperature for 5 minutes. Changes in absorbance at 405 nm with time were measured to evaluate the inhibitory activity.

As a result, IC50 = not smaller than 1 nM and less than 10 nM was observed in compounds No. 63, 64, 65, 143, 174, 256, 264, 272, 311, 354, 319, 349, 358, 395, 401, and 402, and IC50 = not smaller than 10 nM and not greater than 100 nM was observed in compounds No. 37, 50, 84, 115, 117, 119,, 121, 123, 130, 147, 168, 256, 320, 321, 324, 352, 355, 364, 380, 392, 398, 444, 455, 459, 460, 506, 863, 866, and 869.

As hereinabove described, the benzimidazole derivatives of the present invention exhibit a potent

chymase inhibitory activity. Thus, it was revealed that the benzimidazole derivatives of the present invention are clinically applicable inhibitory substances for human chymase activity and can be used for prevention and/or therapy of various diseases in which human chymase is involved.

Example 24. Manufacture of tablets

Tablets comprising, per tablet, the following were manufactured:

Compound (No. 37)	50 mg
Lactose	230 mg
Potato starch	80 mg
Polyvinylpyrrolidone	11 mg
Magnesium stearate	5 mg

The compound of the present invention (the compound in Working Example 2), lactose and potato starch were mixed, and the mixture was evenly soaked in 20% polyvinylpyrrolidone in ethanol. The mixture was filtered through a 20 nm mesh, dried at 45°C, and filtered again through a 15 nm mesh. Granules thus obtained were mixed with magnesium stearate and were compressed into tablets.

Industrial Applicability

The thiobenzimidazole derivatives of the present invention and the medically acceptable salts thereof exhibit a potent activity of inhibiting human chymase. Thus, said thiobenzimidazole derivatives and the medically acceptable salts thereof can be used, as a human chymase inhibitor, as clinically applicable preventive and/or therapeutic agents for inflammatory diseases, allergic diseases, diseases of respiratory organs, diseases of circulatory organs, or diseases of bone/cartilage metabolism.

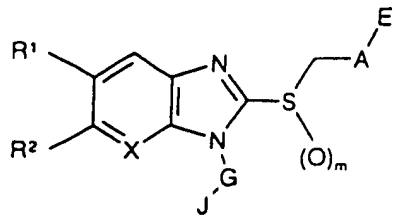
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form or suggestion that that prior art forms part of the common general knowledge in Australia.

It would be appreciated by a person skilled in the art the numerous variations and/or modifications may be made to the invention as shown the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A thiobenzimidazole derivative represented by the following formula (1):



(1)

wherein,

R^1 and R^2, simultaneously or independently of each other, represent a hydrogen atom, a halogen atom, a trihalomethyl group, a cyano group, a hydroxy group, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R^1 and R^2 together form $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ or $-CH_2-CH_2-CH_2-$, in which the carbons may be substituted with one or a plurality of alkyl groups having 1 to 4 carbons;

A represents a single bond, a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, in which the substituent represents a halogen atom, OH, NO_2, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, or a phenoxy group that may be

substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group;

E represents $COOR^3$, SO_3R^3, $CONHR^3$, SO_2NHR^3, a tetrazole group, a 5-oxo-1,2,4-oxadiazole group or a 5-oxo-1,2,4-thiadiazole group in which R^3 represents a hydrogen atom, or a linear or branched alkyl group having 1 to 6 carbons;

G represents a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons that may be interrupted with one or a plurality of O, S, SO_2, and NR^3, in which R^3 is as defined above and the substituent represents a halogen atom, OH, NO_2, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a trihalomethyl group, a trihalomethoxy group, a phenyl group, or an oxo group;

m represents an integer of 0 to 2;

when m is 0 and A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 3 to 6 carbons, a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring;

when m is 0 and A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a

substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring; or

when m is 0 and A is a single bond or when m is 1 or 2, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, in which the substituent represents a halogen atom, OH, NO_2, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a substituted or unsubstituted anilide group, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, a $COOR^3$ group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group; and

X represents CH or a nitrogen atom;

or a medically acceptable salt thereof (hereinafter referred to as "the thiobenzimidazole derivative of the present invention").

2. The thiobenzimidazole derivative according to claim 1 wherein, in the above formula (1), A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of

oxygen, nitrogen and sulfur atoms in the ring, or a medically acceptable salt thereof.

3. The thiobenzimidazole derivative according to claim 1 or 2 wherein, in the above formula (1), A is a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, or a medically acceptable salt thereof.

4. The thiobenzimidazole derivative according to any one of claims 1, 2 and 3 wherein, in the above formula (1), m is 1, or a medically acceptable salt thereof.

5. The thiobenzimidazole derivative according to any one of claims 1, 2 and 3 wherein, in the above formula (1), m is 2, or a medically acceptable salt thereof.

6. The thiobenzimidazole derivative according to any one of claims 1, 2 and 3 wherein, in the above formula (1), m is 0, A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, and J is a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, or a medically acceptable salt thereof.

7. The thiobenzimidazole derivative according to any one of claims 1, 2 and 3 wherein, in the above formula (1), m is 0, A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms in the ring, and J is a substituted or unsubstituted aryl group having 6 to 11 carbons or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a

plurality of oxygen, nitrogen and sulfur atoms in the ring, or a medically acceptable salt thereof.

8. The thiobenzimidazole derivative according to any one of claims 1 to 7 wherein, in the above formula (1), G is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2CO-$, $-CH_2CH_2O-$, $-CH_2CONH-$, $-CO-$, $-SO_2-$, $-CH_2SO_2-$, $-CH_2S-$ or $-CH_2CH_2S-$, or a medically acceptable salt thereof.

9. The thiobenzimidazole derivative according to any one of claims 1 to 8 wherein, in the above formula (1), R^1 and R^2 simultaneously represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R^1 and R^2, independently of each other, represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, a trihalomethyl group, a cyano group, or a hydroxy group, or a medically acceptable salt thereof.

10. The thiobenzimidazole derivative according to any one of claims 1 to 9 wherein, in the above formula (1), E represents COOH or a tetrazole group, or a medically acceptable salt thereof.

11. The thiobenzimidazole derivative according to any one of claims 1 to 10 wherein, in the above formula (1), X represents CH, or a medically acceptable salt thereof.

12. The thiobenzimidazole derivative according to any one of claims 1 to 11 having an activity of inhibiting human chymase, or a medically acceptable salt thereof.

13. A pharmaceutical composition comprising at least one thiobenzimidazole derivative according to any one of claims 1 to 12 or a medically acceptable salt thereof and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition according to claim 13 which is a preventive and/or therapeutic agent of a disease.

15. A preventive and/or therapeutic agent according

to claim 14 wherein said disease is an inflammatory disease, an allergic disease, a disease of respiratory organs, a disease of circulatory organs, or a disease of bone/cartilage metabolism.

16. The thiobenzimidazole derivative according to claim 1 substantially as hereinbefore described with reference to the Examples.

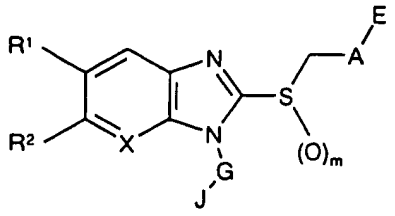
DATED this 28th day of November, 2002

Teijin Limited

by DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

ABSTRACT

The present invention is a thiobenzimidazole derivative represented by the following formula (1)



(1)

or a medically acceptable salt thereof wherein said thiobenzimidazole derivative and a medically acceptable salt thereof have a potent activity of inhibiting human chymase. Thus, they are potential preventive and/or therapeutic agents clinically applicable to various diseases in which human chymase is involved.